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(54) Title: PREPARATION OF 2'FLUORO-2'- ALKYL- SUBSTITUTED OR OTHER OPTIONALLY SUBSTITUTED RIBOFURANOSYL PYRIMIDINES AND PURINES AND THEIR DERIVATIVES

(57) Abstract: The present invention provides (i) processes for preparing a 2'-deoxy-2'fluoro-2'-methyl-D-ribonolactone derivatives, (ii) conversion of intermediate lactones to nucleosides with potent anti-HCV activity, and their analogues, and (iii) methods to prepare the anti-HCV nucleosides containing the 2'-deoxy-2'-fluoro-2'-C-methyl-β-D-ribofuranosyl nucleosides from a preformed, preferably naturally-occurring, nucleoside.

# PREPARATION OF 2'-FLUORO-2'- ALKYL-SUBSTITUTED OR OTHER OPTIONALLY SUBSTITUTED RIBOFURANOSYL PYRIMIDINES AND PURINES AND THEIR DERIVATIVES

This application is being filed on 13 September 2005, as a PCT International Patent application in the name of Pharmasset, Inc., a U.S. national corporation, and Byoung-Kwon Chun, a citizen of South Korea, Peiyuan Wang, a citizen of China, and claims priority to Provisional Patent Application Serial No. 60/609,783, filed on September 14, 2004, Provisional Patent Application Serial No. 60/610,035, filed on September 15, 2004, and Provisional Patent Application Serial Number 60/666,230, filed March 29, 2005, all of which are incorporated by reference in their entireties.

## FIELD OF THE INVENTION

The present invention provides (i) processes for preparing a 2-deoxy-2-fluoro-2-methyl-D-ribonolactone derivatives, (ii) conversion of intermediate lactones to nucleosides with potent anti- HCV activity, and their analogues, and (iii) methods to prepare the anti-HCV nucleosides containing the 2'-deoxy-2'-fluoro-2'-C-methyl-β-D-ribofuranosyl nucleosides from a preformed, preferably naturally-occurring, nucleoside.

## BACKGROUND OF THE INVENTION

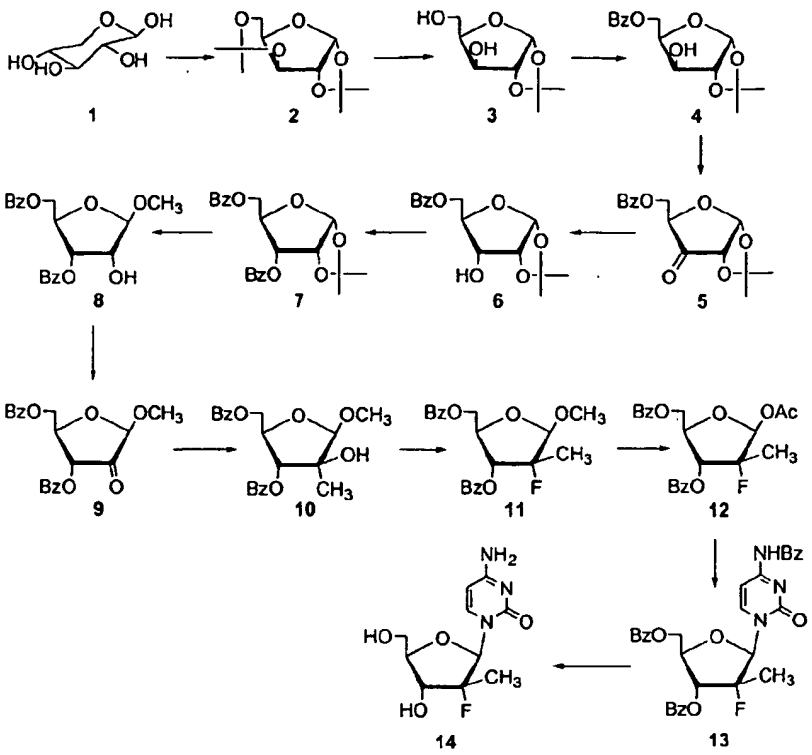
HCV infection has reached epidemic levels worldwide, and has tragic effects on the infected patients. Presently there is no effective treatment for this infection and the only drugs available for treatment of chronic hepatitis C are various forms of alpha interferon (IFN-α), either alone or in combination with ribavirin. However, the therapeutic value of these treatments has been compromised largely due to adverse effects, which highlights the need for development of additional options for treatment.

HCV is a small, enveloped virus in the *Flaviviridae* family, with a positive single-stranded RNA genome of ~9.6 kb within the nucleocapsid. The genome contains a single open reading frame (ORF) encoding a polyprotein of just over 3,000 amino acids, which is cleaved to generate the mature structural and nonstructural viral proteins. ORF is flanked by 5' and 3' non-translated regions (NTRs) of a few hundred nucleotides in length, which are important for RNA

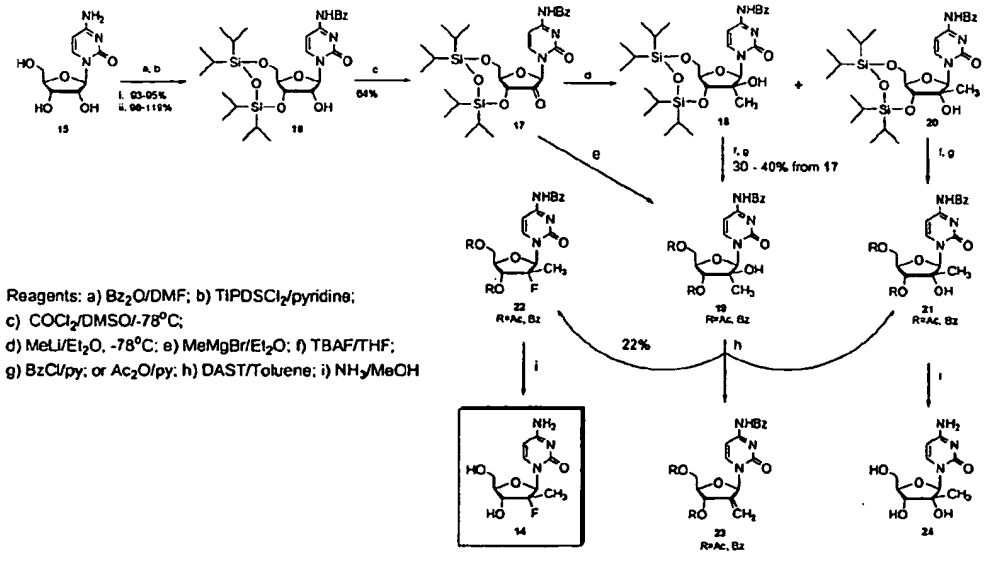
(NTRs) of a few hundred nucleotides in length, which are important for RNA translation and replication. The translated polyprotein contains the structural core (C) and envelope proteins (E1, E2, p7) at the N-terminus, followed by the nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B). The mature structural proteins are generated via cleavage by the host signal peptidase. The junction between NS2 and NS3 is autocatalytically cleaved by the NS2/NS3 protease, while the remaining four junctions are cleaved by the N-terminal serine protease domain of NS3 complexed with NS4A. The NS3 protein also contains the NTP-dependent helicase activity which unwinds duplex RNA during replication. The NS5B protein possesses *RNA-dependent RNA polymerase* (RDRP) activity, which is essential for viral replication. Unlike HBV or HIV, no DNA is involved in the replication of HCV.

U. S. Patent Publication (US 2005/0009737 A1) discloses that 1-(2-deoxy-2-fluoro-2-C-methyl-β-D-ribofuranosyl)cytosine (14) is a potent and selective anti-HCV agent. Previously known synthetic procedures (Schemes 1–3) for this compound are quite inefficient, with very low overall yields and are not amendable to large-scale.

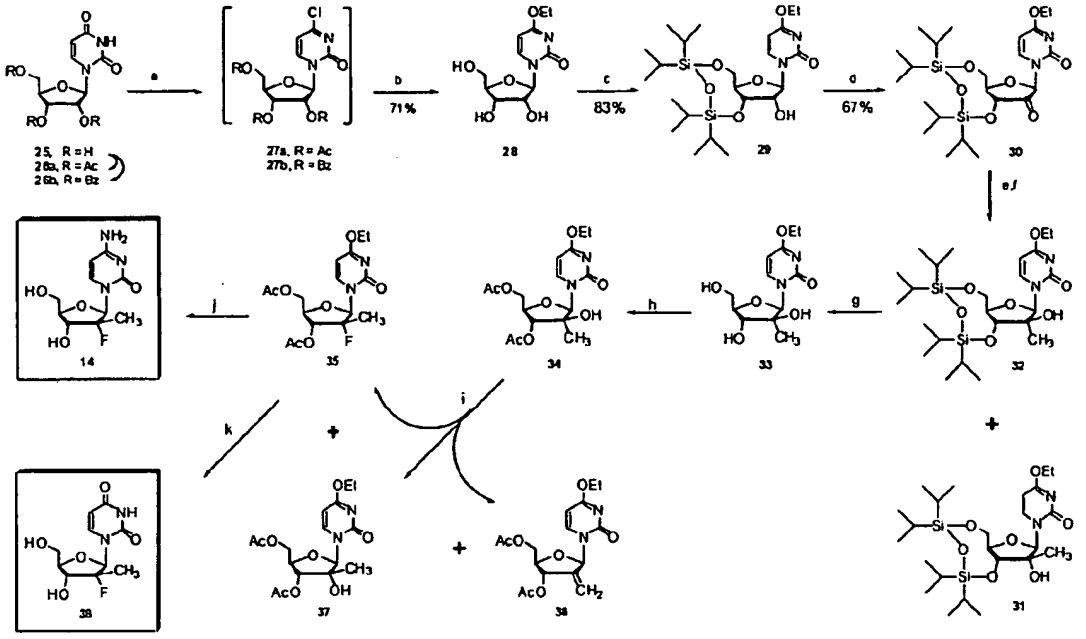
Scheme 1



Scheme 2



Scheme 3



Reagents: a) $SOCl_2/CH_3Cl$, reflux; b) NaOEt/EtOH/ reflux; c) $TIPSDSCl_2$/pyridin/rt;d) $CrO_3/Ac_2O$/pyridine, rt; e) MeLi/$Et_2O$, -78°C; f) MeMgBr/$Et_2O$, -50 °C; g) TBAF/THF;h) $Ac_2O$/py; i) DAST/Toluene; j) $NH_3$/MeOH; k) 1N NaOH/THF/ 60 °C

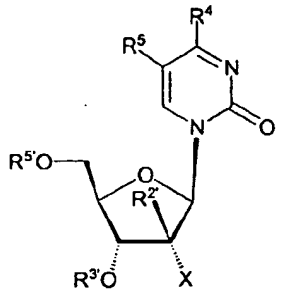
Previously known methods for the preparation of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleosides, and its analogues, from D-xylose, cytidine, or uridine employed DAST or Deoxofluor® for the key fluorination reaction. However, DAST and Deoxofluor® are expensive, hazardous for industrial synthesis, and provide often unreliable results. Therefore, these alkylaminosulfur trifluorides are not suitable for industrial production.

As a part of an effort to find better fluorination conditions, it has been discovered that opening of a cyclic sulfate with non- alkylaminosulfur trifluoride fluorinating agents is an excellent way to synthesize the anti-HCV nucleoside, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine. In addition, it was discovered that this novel synthetic route can be adopted to other nucleosides including the anti-HCV nucleoside, D-2-deoxy-2-fluoro- cytidine (Devos, et al, U.S. Pat. 6,660,721), anti-HBV nucleosides, D and L-2',3'-didehydro-2',3'-dideoxy-2'-fluoro-nucleosides (Schinazi, et al, U.S. Pat. 6,348,587) (I and II, Figure 3) as well as other 2'-substituted nucleosides such as D- and L-FMAU (Su, et al., *J Med. Chem*, 1986, *29*,151-154; Chu, et al., U.S. Pat. 6,512,107).

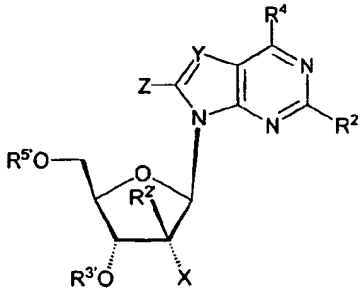
What is needed is a novel and cost effective process for the synthesis of 2-*C*-alkyl-2-deoxy-2-substituted-D-ribopyranosyl nucleosides that have activity against HCV.

## SUMMARY OF INVENTION

The present invention as disclosed herein relates to various intermediates and synthetic methods for the preparation of compounds of general formulas [I] and [II],



I



II

wherein

X is halogen (F, Cl, Br),

Y is N or CH,

Z is, halogen, OH, OR', SH, SR', $NH_2$, NHR', or R'

$R^{2'}$ is alkyl of $C_1$-$C_3$, vinyl, or ethynyl;

$R^{3'}$ and $R^{5'}$ can be same or different H, alkyl, aralkyl, acyl, cyclic acetal such as 2',3'-O-isopropylidene or 2',3-O-benzylidene, or 2',3'-cyclic carbonate.

$R^2$, $R^4$, and $R^5$ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', $N_3$, $NH_2$, NHR', NR'$_2$, NHC(O)OR', lower alkyl of $C_1$-$C_6$, halogenated (F, Cl, Br, I) lower alkyl of $C_1$-$C_6$ such as $CF_3$ and $CH_2CH_2F$, lower alkenyl of $C_2$-$C_6$ such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of $C_2$-$C_6$ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of $C_2$-$C_6$ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of $C_2$-$C_6$, lower alkoxy of $C_1$-$C_6$ such as $CH_2OH$ and $CH_2CH_2OH$, halogenated (F, Cl, Br, I) lower alkoxy of $C_1$-$C_6$,

$CO_2H$, $CO_2R'$, $CONH_2$, $CONHR'$, $CONR'_2$, $CH{=}CHCO_2H$, $CH{=}CHCO_2R'$; and,

R' is an optionally substituted alkyl or acyl of $C_1$-$C_{12}$ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of $C_2$-$C_6$, optionally substituted lower alkenyl of $C_2$-$C_6$, or optionally substituted acyl.

## DETAILED DESCRIPTION

Presently no preventive means against Flaviviridae, including hepatitis C virus (HCV), Dengue virus (DENV), West Nile virus (WNV) or Yellow Fever virus (YFV), infection is available. The only approved therapies are for treatment of HCV infection with alpha interferon alone or in combination with the nucleoside ribavirin, but the therapeutic value of these treatments has been compromised largely due to adverse effects. It was recently discovered that a group of nucleosides, including 2'-deoxy-2'-fluoro-2'-C-methylcytidine, exhibit potent and selective activity against replication of HCV in a replicon system. However, the difficulty of chemical synthesis of this and analogous nucleosides impedes further biophysical, biochemical, pharmacological evaluations mandatory for development of clinical drugs for treatment of Flaviviridae infection.

The present invention provides an efficient preparation of nucleosides and intermediates containing the 2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranosyl moiety.

**Definitions**

The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application. Thus, in a compound such as $R^aXYR^a$, wherein $R^a$ is "independently carbon or nitrogen", both $R^a$ can be carbon, both $R^a$ can be nitrogen, or one $R^a$ can be carbon and the other $R^a$ nitrogen.

As used herein, the terms "enantiomerically pure" or "enantiomerically enriched"refers to a nucleoside composition that comprises at least approximately 95%, and preferably approximately 97%, 98%, 99% or 100% of a single enantiomer of that nucleoside.

As used herein, the term "substantially free of" or "substantially in the absence of" refers to a nucleoside composition that includes at least 85 or 90% by weight, preferably 95% to 98% by weight, and even more preferably 99% to 100% by weight, of the designated enantiomer of that nucleoside. In a preferred embodiment, in the methods and compounds of this invention, the compounds are substantially free of enantiomers.

The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon chain of typically $C_1$ to $C_{10}$, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, pentyl, , isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl, and the like. The term includes both substituted and unsubstituted alkyl groups. Alkyl groups can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate. One or more of the hydrogen atoms attached to carbon atom on alkyl may be replaces by one or more halogen atoms, e.g. fluorine or chlorine or both, such as trifluoromethyl, difluoromethyl, fluorochloromethyl, and the like. The hydrocarbon chain may also be interrupted by a heteroatom, such as N, O or S.

The term "lower alkyl," as used herein, and unless otherwise specified, refers to a $C_1$ to $C_4$ saturated straight or branched alkyl group, including both substituted and unsubstituted forms as defined above. Unless otherwise specifically stated in this application, when alkyl is a suitable moiety, lower alkyl is preferred. Similarly, when alkyl or lower alkyl is a suitable moiety, unsubstituted alkyl or lower alkyl is preferred.

The term "cycloalkyl", as used herein, unless otherwise specified, refers to a saturated hydrocarbon ring having 3-8 carbon atoms, preferably, 3-6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl group may also be substituted on the ring by and alkyl group, such as cyclopropylmethyl and the like.

The terms "alkylamino" or "arylamino" refer to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected," as used herein and unless otherwise defined, refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. Non-limiting examples include: C(O)-alkyl, C(O)Ph, C(O)aryl, $CH_3$, $CH_2$-alkyl, $CH_2$-alkenyl, $CH_2Ph$, $CH_2$-aryl, $CH_2O$-alkyl, $CH_2O$-aryl, $SO_2$-alkyl, $SO_2$-aryl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, and 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

The term "aryl," as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The term includes both substituted and unsubstituted moieties. The aryl group can be substituted with one or more substituents, including, but not limited to hydroxyl, halo, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The terms "alkaryl" or "alkylaryl" refer to an alkyl group with an aryl substituent. The terms "aralkyl" or "arylalkyl" refer to an aryl group with an alkyl substituent, as for example, benzyl.

The term "halo," as used herein, includes chloro, bromo, iodo and fluoro.

The term "acyl ester" or "O-linked ester" refers to a carboxylic acid ester of the formula C(O)R' in which the non-carbonyl moiety of the ester group, R', is a straight or branched alkyl, or cycloalkyl or lower alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen (F, Cl, Br, I), $C_1$ to $C_4$ alkyl or $C_1$ to $C_4$ alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butyl silyl) or diphenylmethylsilyl. Aryl groups in the esters optimally include a phenyl group.

The term "acyl" refers to a group of the formula R''C(O)-, wherein R'' is a straight or branched alkyl, or cycloalkyl, amino acid, aryl including phenyl, alkylaryl,

aralkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl; or substituted alkyl (including lower alkyl), aryl including phenyl optionally substituted with chloro, bromo, fluoro, iodo, $C_1$ to $C_4$ alkyl or $C_1$ to $C_4$ alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxy-trityl, substituted benzyl, alkaryl, aralkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl. Aryl groups in the esters optimally comprise a phenyl group. In particular, acyl groups include acetyl, trifluoroacetyl, methylacetyl, cyclopropylacetyl, cyclopropyl carboxy, propionyl, butyryl, isobutyryl, hexanoyl, heptanoyl, octanoyl, neo-heptanoyl, phenylacetyl, 2-acetoxy-2-phenylacetyl, diphenylacetyl, α-methoxy-α-trifluoromethyl-phenylacetyl, bromoacetyl, 2-nitro-benzeneacetyl, 4-chloro-benzeneacetyl, 2-chloro-2,2-diphenylacetyl, 2-chloro-2-phenylacetyl, trimethylacetyl, chlorodifluoroacetyl, perfluoroacetyl, fluoroacetyl, bromodifluoroacetyl, methoxyacetyl, 2-thiopheneacetyl, chlorosulfonylacetyl, 3-methoxyphenylacetyl, phenoxyacetyl, tert-butylacetyl, trichloroacetyl, monochloro-acetyl, dichloroacetyl, 7H-dodecafluoro-heptanoyl, perfluoro-heptanoyl, 7H-dodeca-fluoroheptanoyl, 7-chlorododecafluoro-heptanoyl, 7-chloro-dodecafluoro-heptanoyl, 7H-dodecafluoroheptanoyl, 7H-dodeca-fluoroheptanoyl, nona-fluoro-3,6-dioxa-heptanoyl, nonafluoro-3,6-dioxaheptanoyl, perfluoroheptanoyl, methoxybenzoyl, methyl 3-amino-5-phenylthiophene-2-carboxyl, 3,6-dichloro-2-methoxy-benzoyl, 4-(1,1,2,2-tetrafluoro-ethoxy)-benzoyl, 2-bromo-propionyl, omega-aminocapryl, decanoyl, n-pentadecanoyl, stearyl, 3-cyclopentyl-propionyl, 1 -benzene-carboxyl, O-acetylmandelyl, pivaloyl acetyl, 1-adamantane-carboxyl, cyclohexane-carboxyl, 2,6-pyridinedicarboxyl, cyclopropane-carboxyl, cyclobutane-carboxyl, perfluorocyclohexyl carboxyl, 4-methylbenzoyl, chloromethyl isoxazolyl carbonyl, perfluorocyclohexyl carboxyl, crotonyl, 1-methyl-1H-indazole-3-carbonyl, 2-propenyl, isovaleryl, 1-pyrrolidinecarbonyl, 4-phenylbenzoyl. When the term acyl is used, it is meant to be a specific and independent disclosure of acetyl, trifluoroacetyl, methylacetyl, cyclopropylacetyl, propionyl, butyryl, isobutyryl, hexanoyl, heptanoyl, octanoyl, neo-heptanoyl, phenylacetyl, diphenylacetyl, ct-trifluoromethyl-phenylacetyl, bromoacetyl, 4-chloro-benzeneacetyl, 2-chloro-2,2-diphenylacetyl, 2-chloro-2-phenylacetyl, trimethylacetyl, chlorodifluoroacetyl, perfluoroacetyl,

fluoroacetyl, bromodifluoroacetyl, 2-thiopheneacetyl, tert-butylacetyl, trichloroacetyl, monochloro-acetyl, dichloroacetyl, methoxybenzoyl, 2-bromo-propionyl, decanoyl, n-pentadecanoyl, stearyl, 3-cyclopentyl-propionyl, 1 -benzene-carboxyl, pivaloyl acetyl, 1-adamantane-carboxyl, cyclohexane-carboxyl, 2,6-pyridinedicarboxyl, cyclopropane-carboxyl, cyclobutane-carboxyl, 4-methylbenzoyl, crotonyl, 1-methyl-1H-indazole-3-carbonyl, 2-propenyl, isovaleryl, 4-phenylbenzoyl.

The term "lower acyl" refers to an acyl group in which R", above defined, is lower alkyl.

The term " natural nucleic base" and " modified nucleic base" refer to "purine" or "pyrimidine" bases as defined below.

The term "purine" or "pyrimidine" base includes, but is not limited to, adenine, $N^6$-alkylpurines, $N^6$-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), $N^6$-benzylpurine, $N^6$-halopurine, $N^6$-vinylpurine, $N^6$-acetylenic purine, $N^6$-acyl purine, $N^6$-hydroxyalkyl purine, $N^6$-allcylaminopurine, $N^6$-thioallcyl purine, $N^2$-alkylpurines, $N^2$-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, $C^5$-alkylpyrimidines, $C^5$-benzylpyrimidines, $C^5$-halopyrimidines, $C^5$-vinylpyrimidine, $C^5$-acetylenic pyrimidine, $C^5$-acyl pyrimidine, $N^4$-acetylcytosine, $N^4$-benzoylcytosine, $N^4$-alkyl pyrimidine, $C^5$-hydroxyalkyl purine, $C^5$-amidopyrimidine, $C^5$-cyanopyrimidine, ,$C^5$-iodopyrimidine, $C^6$-lodo-pyrimidine, $C^5$-Br-vinyl pyrimidine, $C^6$-Br-vinyl pyriniidine, $C^5$-nitropyrimidine, $C^5$-amino-pyrimidine, $N^2$-alkylpurines, $N^2$-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

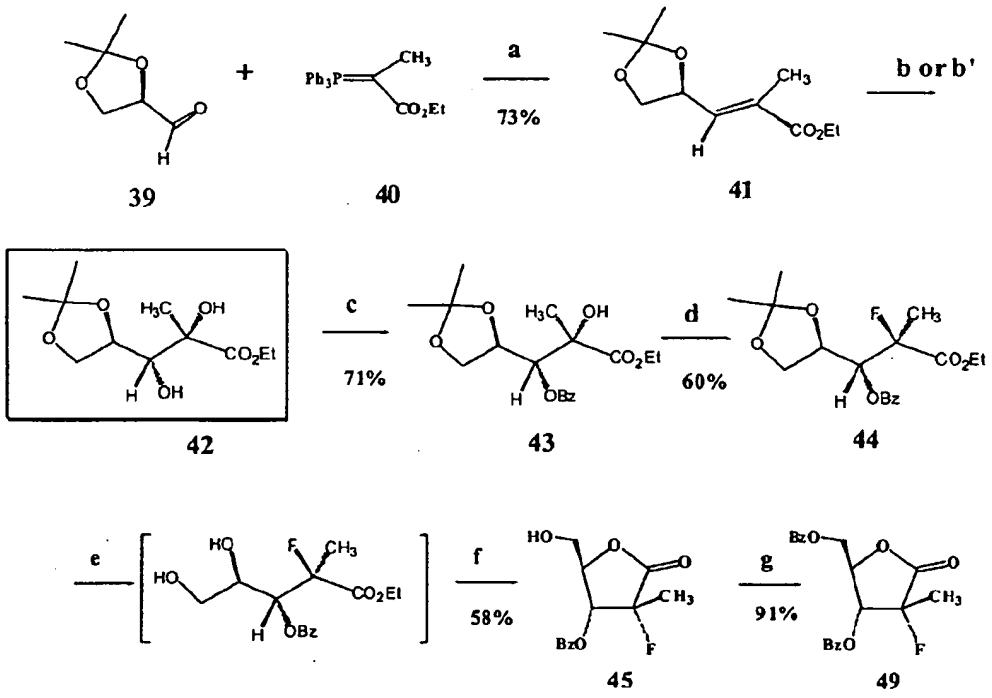
The term "amino acid" includes naturally occurring and synthetic $\alpha$, $\beta$ $\gamma$ or $\delta$ amino acids, and includes but is not limited to, amino acids found in proteins, i.e. glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan,

proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine. In a preferred embodiment, the amino acid is in the L-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleucinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleucinyl, β-prolinyl, β-phenylalaninyl, β-tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl. When the term amino acid is used, it is considered to be a specific and independent disclosure of each of the esters of α, β γ or δ glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in the D and L-configurations.

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a compound which, upon administration to a patient, provides the active compound. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art. Pharmaceutically acceptable salts may also be acid addition salts when formed with a nitrogen atom. Such salts are derived from pharmaceutically acceptable inorganic or organic acids, such as hydrochloric, sulfuric, phosphoric, acetic, citric, tartaric, and the like. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound.

Applicants have developed a novel, practical and efficient process for the synthesis of 2-*C*-alkyl-2-deoxy-2-substituted-D-ribofuranose derivatives, the key intermediates to **14** (Scheme 1) and derivatives and analogues thereof using or without using chiral catalysts. The key step in the synthesis of **14** is asymmetric conversion of **41** to **42** using chiral catalysts (Scheme 4). The previous disclosed synthesis of **42** required Sharpless AD catalysts, such as dihydroquinidine (DHQD) and derivatives. The present invention as disclosed herein relates to the stereoselective preparation of **41** to **42** using osmium, osmate or permanganate without chiral catalysts. The applicants in this present invention also develop a practical and efficient process for the synthesis of **49** from **42** by using the nucleophilic opening of the cyclic sulfate **50** (Scheme 6) in highly stereospecific and regioselective manner. The procedure depicted in Schemes 4, 5 and 6 are the current method of choice for preparative synthesis of **14** and related derivatives.

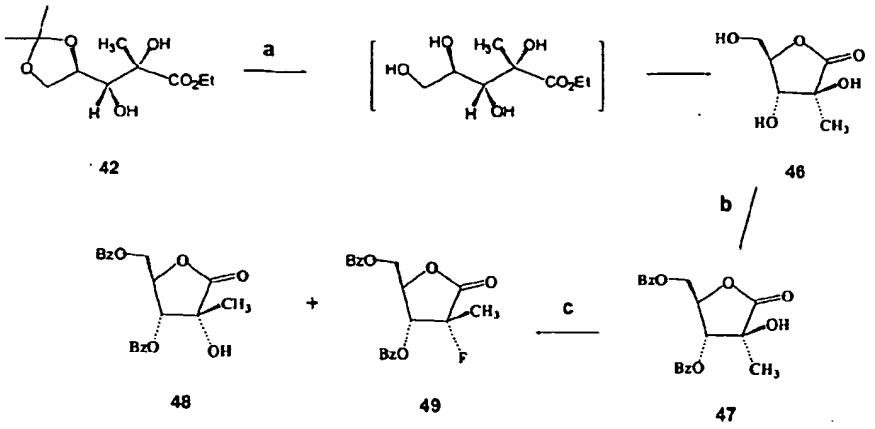
Scheme 4




39 40 41 42 43 44 45 49

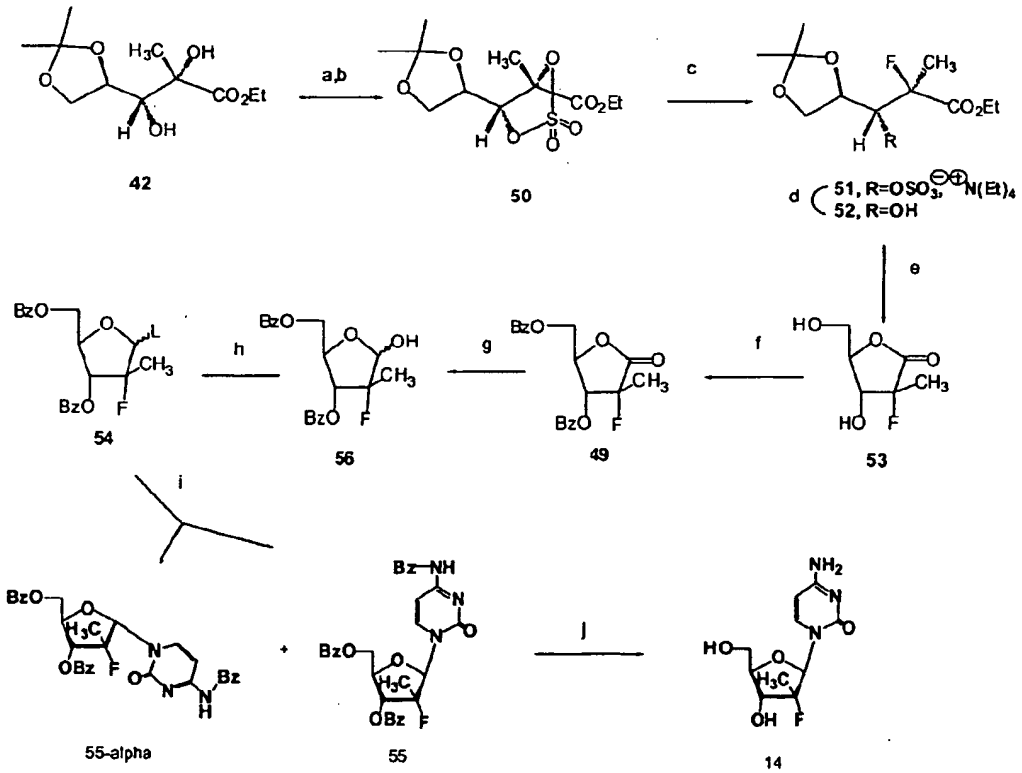
**Reagent: (a) $CH_2Cl_2$, rt, 12h (b) AD-mix-β, 1:1 *t*-BuOH-$H_2O$, $MeSO_2NH_2$, 0 °C, 24 h;or (b'): stereoselective dihydroxylation without chiral catalysts; (c) BzCl/Py, rt; (d) DAST/THF, rt; (e) MeCN/$H_2O$/$CF_3CO_2H$, 80-90 °t azeotropic distillation; (g) BzCl/Py/$CH_2Cl_2$, rt.**

Scheme 5



Reagent: (a) HCl/EtOH (b) BzCl/Py (c) DAST

Scheme 6

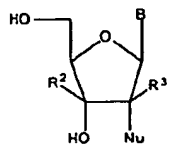


Reagent: (a) $SOCl_2$, $Et_3N$, $CH_2Cl_2$; (b) TEMPO-NaOCl, (c) TEAF (d) HCl (e) AcOH or Dowex-$H^+$ (f) BzCl/Py; (g) LiAl(O Bu-t)$_3$H; (h)Ac2O ; (i) silylated bases/Vorbruggen condition; (j) $NH_3$/MeOH

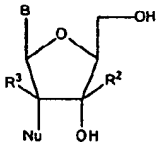
I. PREPARATION OF THE COMPOUNDS

**(i) Synthesis of the cyclic sulfite (IIIa) and cyclic sulfate (IIIb)**

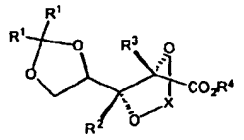
This invention relates to the process for the preparation of the 2'-F-nucleosides and other 2'- substituted nucleosides of the general formula **IB and IB-L**- by using the nucleophilic opening of the cyclic sulfite, **IIIa** (X = SO), sulfate, **IIIb** ($X = SO_2$), of the formula, **III** in highly stereospecific and regioselective manner, via the lactones of the formula, **IV.**



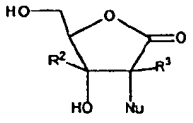
IB



IB-L



III



IV

Wherein the formula IB, IB-L, III, IV has following specifications:

$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including, but not limited to methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl; alternatively $R^1$ is a part of cyclic alkylene including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclic pentyl or cyclic hexanyl group;

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including, but not limited to methyl, hydroxymethyl, methoxymethyl, halomethyl including, but not limited to fluoromethyl, ethyl, propyl, optionally substituted ethenyl including, but not limited to vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including, but not limited to haloethnyl (F-C≡C), optionally substituted allyl including, but not limited to haloallyl (FHC=CH-$CH_2$-);

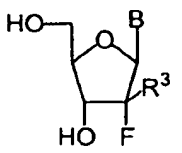
$R^4$ is independently hydrogen, aryl including, but not limited to phenyl, aryl alkyl including, but not limited to benzyl, lower alkyl including, but not

limited to, methyl, ethyl, propyl. Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, OR or NR where R is acyl including, but not limited to acetyl, benzoyl, arylalkyl including but not limited to benzyl, lower alkyl including, but not limited to, methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl including, but not limited to, methyl, ethyl, propyl;

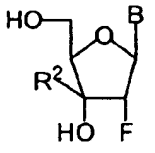
X is $SO_2$, SO, or CO; and

B is a natural or modified nucleic base.

In one embodiment, formula, **IB** is:




**Ia**



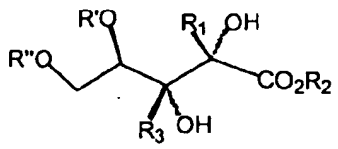

**Ib**

wherein,

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including, but not limited to methyl, hydroxymethyl, methoxymethyl, halomethyl including, but not limited to fluoromethyl, ethyl, propyl, optionally substituted ethenyl including, but not limited to vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including, but not limited to haloethnyl (F-C≡C), optionally substituted allyl including, but not limited to haloallyl (FHC=CH-$CH_2$-);

B is a natural or modified nucleic base.

The present invention as disclosed herein relates to processes for the synthesis of a compound, 2-alkyl-4,5-di-O-protected-2,3-dihydroxy-pentanoic-acid ester of the following general formula **42B**, which is the important intermediate in the synthesis of anti-HCV nucleosides of general formulas **[I]** and **[II]** (below).



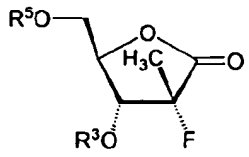

**42B**

wherein R', R" = isopropylidene, benzylidene or cyclohexylidene or a like, or a part of cyclic group including ethylene ($-CH_2CH_2-$), or trimethylene ($-CH_2CH_2CH_2-$) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently lower alkyl of $C_1$-$C_6$, or aryl of $C_6$-$C_{20}$),benzyl and other optionally substituted benzyl, trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups; or H, acetyl, benzoyl and other optionally substituted acyl (R' and R" are –C(O)-R, wherein R can be lower alkyl of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$, benzyl or other optionally substituted benzyl);

$R_1$, $R_2$ are independently hydrogen, aryl ($C_6$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl ($FHC=CH-CH_2-$); and

$R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, but not limited to benzyl, lower alkyl ($C_{1-6}$) including methyl, ethyl, or propyl.

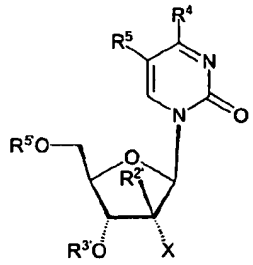
The invention as disclosed herein also relates to processes for making compounds of the following general formula **49B**, which are prepared from 2-alkyl-4,5-di-O-protected-2,3-dihydroxy-pentanoic-acid ester derivatives of general formula **[42B]**.



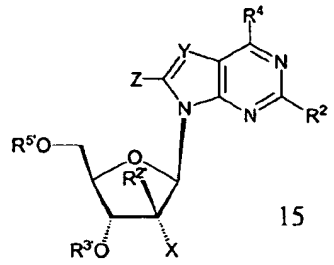

**49B**

wherein $R^3$ and $R^5$ can be independently H, $CH_3$, Ac, Bz, pivaloyl, or 4-nitrobenzoyl, 3-nitrobenzoyl, 2-nitrobenzoyl, 4-chlorobenzoyl, 3-chlorobenzoyl, 2-

chlorobenzoyl, 4-methylbenzoyl, 3-methylbenzoyl, 2-methylbenzoyl, para-phenylbenzoyl, and other optionally substituted acyl ($R^3$ and $R^5$ are –C(O)-R, R can be independently lower alkyl of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$), benzyl, 4-methoxybenzyl and other optionally substituted benzyl ($R^3$ and $R^5$ can be independently aryl of $C_6$-$C_{20}$), trityl, trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups ($R^3$ and $R^5$ can be independently alkyl of $C_1$-$C_{10}$), or $R^3$ and $R^5$ are linked through -$SiR_2$-O-$SiR_2$- or –$SiR_2$-, wherein R is a lower alkyl group such as Me, Et, *n*-Pr or *i*-Pr.



I



II

wherein

X is halogen (F, Cl, Br),

Y is N or CH,

Z is, halogen, OH, OR', SH, SR', $NH_2$, NHR', or R'

$R^{2'}$ is alkyl of $C_1$-$C_3$, vinyl, or ethynyl

$R^{3'}$ and $R^{5'}$ can be same or different H, alkyl, aralkyl, acyl, cyclic acetal such as 2',3'-O-isopropylidene or 2',3-O-benzylidene, or 2',3'-cyclic carbonate.

$R^2$, $R^4$, $R^5$ and $R^6$ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', $N_3$, $NH_2$, NHR', NR'', NHC(O)OR', lower alkyl of $C_1$-$C_6$, halogenated (F, Cl, Br, I) lower alkyl of $C_1$-$C_6$ such as $CF_3$ and $CH_2CH_2F$, lower alkenyl of $C_2$-$C_6$ such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of $C_2$-$C_6$ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of $C_2$-$C_6$ such as C≡CH, halogenated (F, Cl,

Br, I) lower alkynyl of $C_2$-$C_6$, lower alkoxy of $C_1$-$C_6$ such as $CH_2OH$ and $CH_2CH_2OH$, halogenated (F, Cl, Br, I) lower alkoxy of $C_1$-$C_6$, $CO_2H$, $CO_2R'$, $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$; and,

R' and R" are the same or different and are optionally substituted alkyl of $C_1$-$C_{12}$ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of $C_2$-$C_6$, optionally substituted lower alkenyl of $C_2$-$C_6$, or optionally substituted acyl.

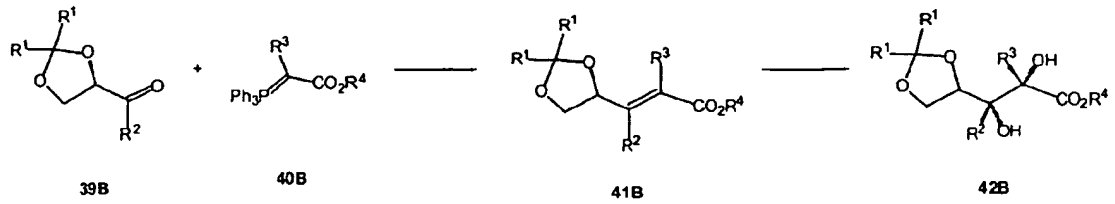
The reaction of the cyclic sulfate ester, **50** (Scheme 6) with tetraethylammonium fluoride or tetramethylammonium fluoride **51**(Scheme 6) quantitatively generated the fluorinated sulfate, in highly stereospecific and regioselective manner. Following acid catalyzed cyclization afforded the 2'-fluoro-2-*C* -methyl-γ-ribonolactone, **53** in high yield.

The present invention is based on this discovery and provides a process for the preparation of the 2'-deoxy-2'-substituted nucleosides, **I** and **II**, using the reactions described herein.

(2S, 3R, 4R)-4,5-O-alkylidene-2-dimethyl-2, 3, 4, 5-tetrahydroxy-2-methyl-pentanoic acid ethyl ester (**42B**), can be prepared by asymmetric dihydroxylation (AD) or stereoselective dihydroxylation of the Wittig product **41** with or without chiral catalysts. Wittig product **41**, in turn, can be prepared readily from the protected (**R**) glyceraldehyde (Schemes 7, 8), where $R^1$ is independently a lower alkyl ($C_1$-$C_6$) including, but not limited to methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl. Or $R^1$ is a part of cyclic group including ethylene ($-CH_2CH_2-$), or trimethylene ($-CH_2CH_2CH_2-$) forming cyclopentyl or cyclohexanyl group, respectively. $R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including, but not limited to methyl, hydroxymethyl, methoxymethyl, halomethyl including, but not limited to fluoromethyl, ethyl, propyl, optionally substituted ethenyl including, but not limited to vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including, but not limited to haloethnyl (F-C≡C), optionally substituted allyl including, but not limited to haloallyl ($FHC=CH-CH_2-$); and $R^4$ is acyl including, but not limited to acetyl, benzoyl, arylalkyl including but not limited to benzyl, lower alkyl ($C_{1-10}$) including, but not limited to, methyl, ethyl,

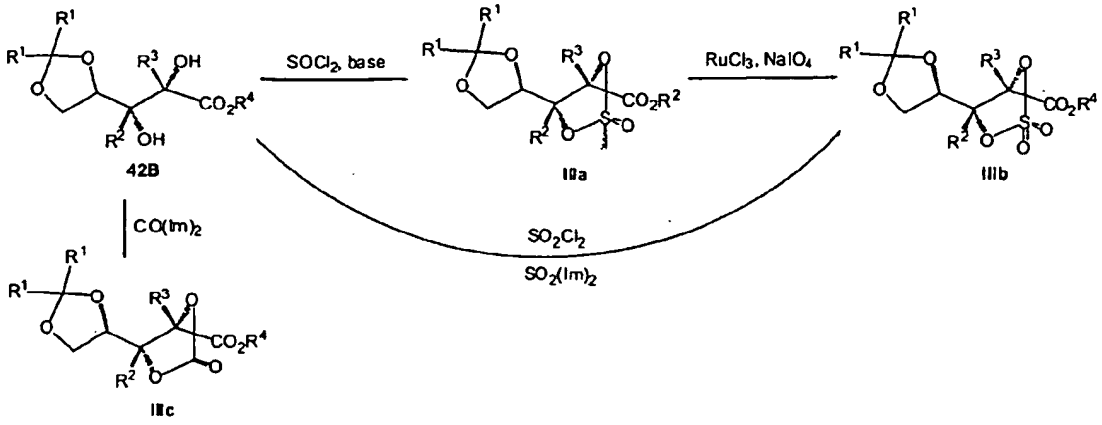
propyl, $CH_2R$ where R is hydrogen, lower alkyl ($C_{1-10}$) including, but not limited to, methyl, ethyl, propyl.

Scheme 7




The diol (**42B**) can be converted to the cyclic sulfite (**IIIa**) by treatment with thionyl chloride ($SOCl_2$) in presence of alkylamine such as triethylamine, diisopropyl ethylamine, or pyridine, which can then be oxidized using the oxidants selected from a first group consisting of $RuCl_3$, $KMNO_4$, and TEMPO or a combination of the first group and one of the second group consisting of $NaIO_4$, $KIO_4$, $HIO_4$, mCPBA, NaOCl, and oxone. The solvent of this step is selected from one or more of the group consisting of chloroform, methylene chloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, benzene, and toluene, alone or in combination with water. (Gao Y et al *J. Am. Chem. Soc.* 1988, *110,* 7538-7539, Berridge et al *J. Org. Chem.* 1990, *55,* 1211-1217). It is also possible that the diol is directly converted to the cyclic sulfate (**Vb**) by treatment with sulfurylchloride, or sulfuryl diimidazole. On the other hand, the diol **42B** can be converted to the cyclic carbonate(**IIIc**) by treatment with carbonyl diimidazole or carbonyl dimethoxide (Scheme 8) (Chang, et al *Tetrahedron Lett.* 1996, *37,* 3219-3222).

Scheme 8




**(ii) Synthesis of the substituted 2-deoxy-D-ribono-γ-latone, 53B**

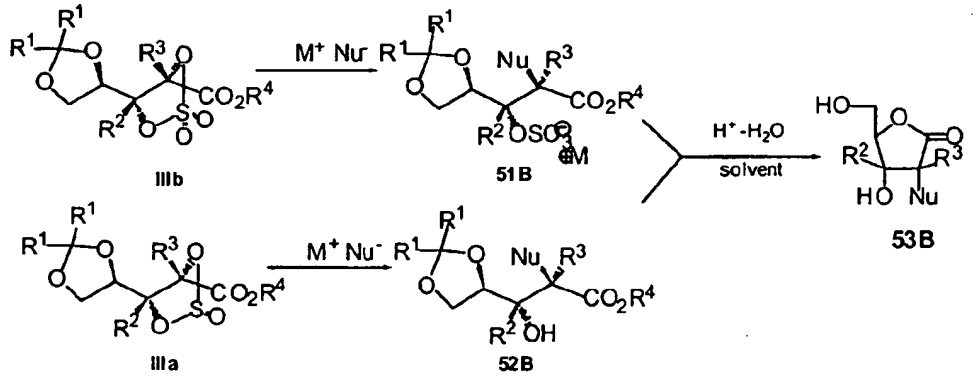
The cyclic sulfate (IIIb, Scheme 8) can be converted to the fluorinated sulfate ester of the formula, **51B** (Scheme 9), in high yield and with high regioselectivity and stereospecificity, by treatment with tetraalkylammonium fluoride including, but not limited to tetramethylammonium fluoride (TMAF), tetraethylammonium fluoride (TEAF), or tetrabutylammomnium fluoride (TBAF), or tris(dimehtylamino)sulfur (trimethylsilyl)difluoride (TAS-F) (Fuentes J, et al *Tetrahedron lett.* 1998, *39*, 7149-7152) in a protic polar solvent such as acetone, tetrahydrofuran, *N,N*-dimethylformamide, or acetonitrile (Scheme 9). Metal fluorides such as silver fluoride (AgF), potassium fluoride (KF), cesium fluoride (CsF), or rubidium fluoride (RbF), can be used alone or with catalytic amount of tetraalkylammonium fluoride, crown-ether, diglyme, or polyethylene glycol, or other phase transfer catalyst.

The cyclic sulfate (**IIIb**) can be converted to other 2-substituted sulfates of the formula **51B** by treatment with NaBH4, tetraalkylammonium chloride, tetraalkylammonium bromide, NaN3 or LiN3, $NH_4OR$, $NH_4SCN$, $CF_3I$-tetrakis(dimethylamino)-ethylene (TDAE), and tetraalkylammonium nitrate (Gao et al J. Am. Chem. Soc. 1988, 110, 7538-7539), KCN, LiCu(R)2 where R is methyl, ethyl, ethylenyl, or ethnyl. Similarly, the cyclicsulfite (**IIIa**) can be converted to the substituted ester **52B** (Chang et al. Tetrahedron Lett. 1996, 37, 3219-3222). Then compounds of the formula **51B and 52B** can be converted to the substituted lactones

of the formula **53B** by treatment with an acid in $H_2O$-containing organic solvent such as methanol, ethanol, or acetonitrile.

In Formula **53B**, $R^2$, $R^3$ is independently hydrogen, a lower alkyl ($C_1$-$C_6$) including, but not limited to methyl, hydroxymethyl, methoxymethyl, halomethyl including, but not limited to fluoromethyl, ethyl, propyl, optionally substituted ethenyl including, but not limited to vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including, but not limited to haloethnyl (F-C≡C), optionally substituted allyl including, but not limited to haloallyl (FHC=CH-$CH_2$-). Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or $NR_2$ where R is acyl including, but not limited to acetyl, benzoyl, arylalkyl including but not limited to benzyl, lower alkyl ($C_{1-10}$) including, but not limited to methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl ($C_{1-10}$) including, but not limited to methyl, ethyl, propyl.

Scheme 9

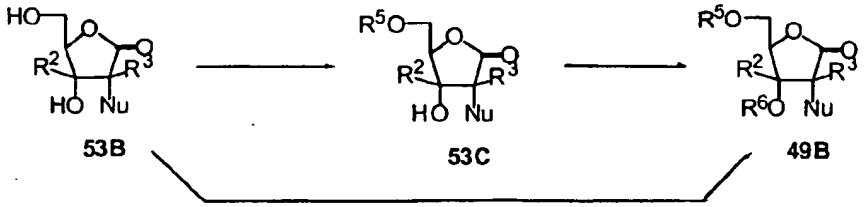



**(iii) The protection of the D-ribono-γ-latone, 53B**

**53B** can be selectively protected with appropriate protection agents to the 5-protected lactones of the formula **53C** with an appropriate base in an appropriate solvent. The protecting group includes, but is not limited to the following: trityl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyloxymethyl, benzoyl, toluoyl, 4-phenyl benzoyl, 2-, 3-, or 4-nitrobenzoyl, 2-, 3-, or 4-chlorobenzoyl, other substituted benzoyl. The base includes, but is not limited to the following: imidazole, pyridine, 4-(dimethylamino)pyridine, triethytlamine, diisopropylethylamine, 1,4-

diazabicyclo[2,2,2]-octane. The solvent includes, but is not limited to the following: pyridine, dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran.

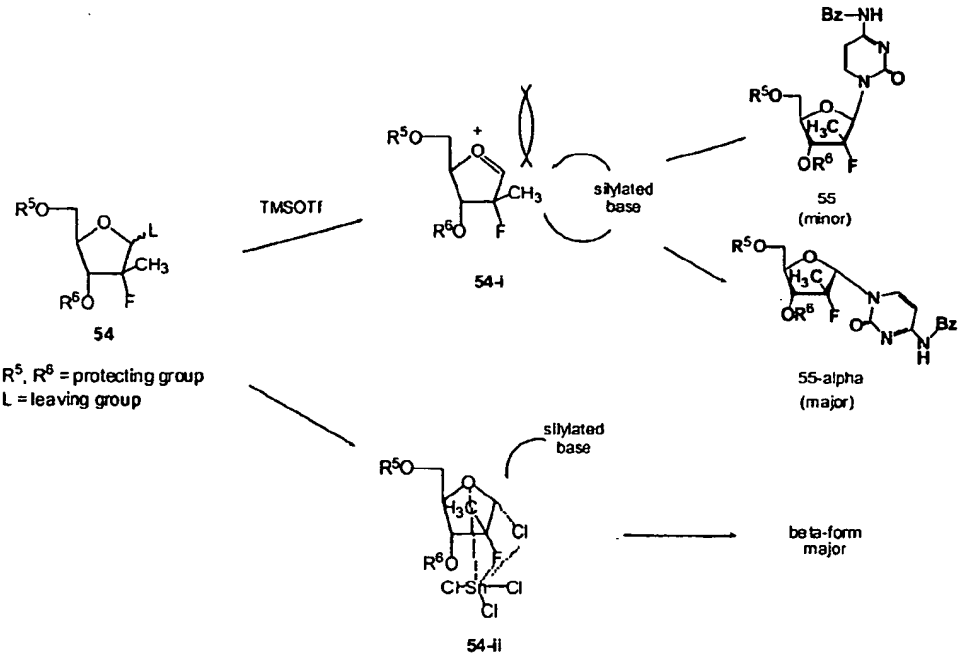
Scheme 10




Alternatively, the lactone **53B** can be fully protected with appropriate protection agents with an appropriate base in an appropriate solvent. The protecting group ($R^5$, $R^6$) includes, but is not limited to the following: methoxymethyl, methoxyethyl, benzyloxymethyl, ethoxymethyl, trityl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, acyl including acetyl, pivaloyl, benzoyl, toluoyl, 4-phenyl benzoyl, 2-, 3-, or 4-nitrobenzoyl, 2-, 3-, or 4-chlorobenzoyl, other substituted benzoyl. The base includes, but is not limited to the following list: imidazole, pyridine, 4-(dimethylamino)pyridine, triethytlamine, diisopropylethylamine, 1,4-diazabicyclo[2,2,2]octane. The solvent includes, but is not limited to pyridine, dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran (Scheme 10).

**(iv) Complexation directed β-glycosylation**

Scheme 10a




Coupling of 2-deoxy-2-fluoro-2-*C*-methyl-ribofuranoside (**54**: Nu=F, $R^3$=Me, $R^5$=$R^6$=pivaloyl) with silylated $N^4$-benzoylcytosine in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in $CHCl_3$ gave a mixture of α/β-anomers with a ratio of 2/1 in favor of α-isomer. However, β-anomer was obtained as major product (α/β = 1/4.9) in the same reaction catalyzed by $SnCl_4$ under similar conditions. Possible mechanisms are proposed in Scheme 10A ($R^5$ and $R^6$ are O-protecting groups that can be acyl or silyl or alkyl or aralkyl with $C_{1\text{-}20}$). Treatment of **54** with silylated $N^4$-benzoylcytosine in the presence of TMSOTf in $CHCl_3$ formed an oxonium intermediate **54-i**. Silylated base could attack **54-1** from up-side to give β-anomer **55B** or from bottom to provide α-anomer **55B-alpha**. Because of stereohinderance at up-side caused by 2-methyl group, silylated base attacked intermediate **54-i** mainly from bottom (less stereohindered side) to afford a mixture of α/β-anomers with a ratio of 2/1 in favor of α-anomer. While treatment of **54** with silylated $N^4$-benzoylcytosine in the presence of $SnCl_4$ , a complex **54-ii** was formed instead of oxonium **54-i**. Silyated $N^4$-benzoylcytosine attacked **54-ii** from less

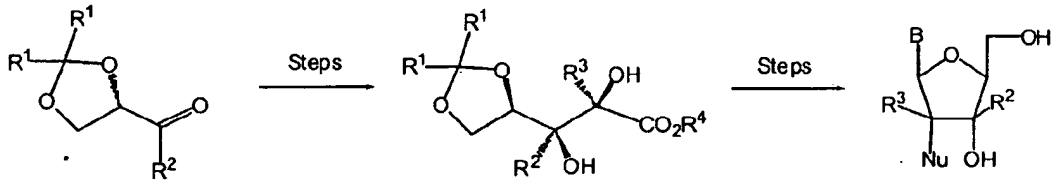
stereohindered up-side to give a mixture of α/β-anomers with a ratio of 1/5 in favor of β-anomer.

Compound **54** can be made from the protected lactone of the formula, **49B**, which can be reduced with DIBAL-H or lithium tri-*tert*-butoxyaluminum hydride and other hydride reducing agent to the lactol, which can then converted either to the acylate by acylation with acyl halide, or acyl anhydride, in presence of an appropriate base in an appropriate solvent. Acyl halide or acyl anhydride includes, but is not limited to the following list: acetic chloride, optionally substituted benzoyl chloride, acetic anhydride, optionally substituted benzoyl anhydride. The base includes, but is not limited to the following: imidazole, pyridine, 4-(dimethylamino)pyridine, triethytlamine, diisopropylethylamine, 1,4- diazabicyclo[2,2,2]octane. The solvent includes, but is not limited to the following list: pyridine, dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran.

**(v) Synthesis of the L-nucleosides, IB-L**

The processes for the D-series of the formula **I** and **II** can be used for preparation of the L-nucleosides of the formula, **IB-L** from the (S)-glyceraldehydes (Scheme 11).

Scheme 11




(S)-glyceraldehyde

**42-L**

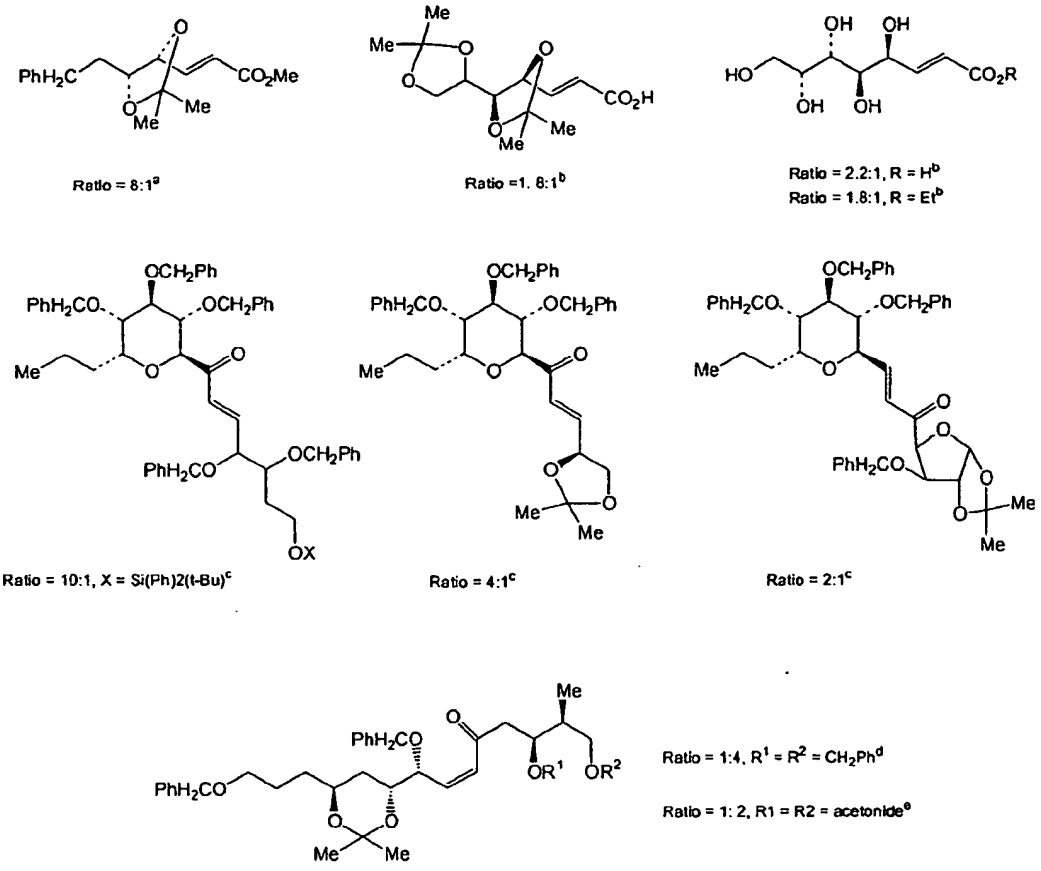
**IB-L**

**(vi) Synthesis of 2-alkyl-4,5-di-O-protected-2, 3-dihydroxy-pentanoic acid**

Currently, the most preferable procedure for the synthesis of nucleosides of general structures **I** and **II** is the preparation of a derivative of the 2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranosyl moiety of **I** and **II** as shown in Scheme 4, Scheme 5 and Scheme 6, above through (i) synthesis of the intermediate, derivatives of 2-alkyl-4,5-di-O-protected-2,3-dihydroxy-pentanoic-acid ester of general structure I, (ii)

conversion of **42B** into the 3,5-protected 2-deoxy-2-fluoro-2-*C*-methyl-D-ribono-γ-latone of general structure **49B**, and (iii) conversion of **49B** into purine and pyrimidine nucleosides of general structures of **I** and **II**. The key step in Scheme 4 is the stereoselective osmium catalyzed dihydroxylation of olefinic intermediate **41** into **42** in the presence of the expensive Sharpless AD catalyst. Instead of the Sharpless catalyst, if other chiral compounds such as L-quinidine are used, the reaction also goes smoothly giving the desired **42**. Kishi et al. have proposed that in $OsO_4$ dihydroxylation of allylic alcohol derivatives (esters, ethers, acetals or ketals), the major course of reaction would occur on the face of the olefinic bond opposite to that of the preexisting hydroxyl or alkoxyl group, (Tetrahedron Lett, 1983, *24*, 3943). Some examples are shown in Scheme 12 (Tetrahedron Lett, 1983, *24*, 3947). In every case, the major product arose from addition of $OsO_4$ from the *anti* side of the oxygen on the neighboring secondary carbon. However, stereoselectivity is not high enough for preparative synthesis.

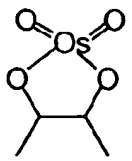
Scheme 12



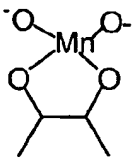

Encouraged by Kishi's rule, which presents that the stereochemistry is formulated as arising from the preferential approach of osmium tetroxide to occur on the face of the olefinic bond opposite to that of the preexisting hydroxyl or alkoxyl group, dihydroxylations of **41** under the original conditions but without any chiral catalysts, including Sharpless AD catalyst, were conducted. Dihydroxylation of **41** using $Ke_3Fe(CN)_6/K_2OsO_2(OH)_4/K_2CO_3$ system without chiral catalysts gives the product in 77% yield, which product is a 5:1 mixture of isomers with the predominant isomer being the desired **42**. The reaction of olefin **41** with $OsO_4$ using N-methylmorpholine N-oxide (NMO) as the oxidant without chiral catalysts gave a 5:1 mixture of **42** and its isomer in 79% yield. Most surprisingly, when t-butylhydroperoxide (TBHP) is used as oxidant in the presence of catalytic amount of $OsO_4$ in acetone and ammonium acetate as buffer (the reagent combination was used in the synthesis of alditols by Masamune and Sharpless (J. Org. Chem, 1982, *47*,

1373)), the crystalline product isolated is the virtually pure desired **42**. This procedure is therefore far superior to the $OsO_4$/NMO and $Fe(CN)_6^{3-}$ methods. At 10 mmolar scale, the desired diol **42** is formed exclusively, and is isolated in 87% yield. No contamination by the other isomer was detected in this product by vigorous $^1H$ NMR analyses.

It is well known that in $OsO_4$ oxidation the intermediate is cyclic osmate **V** (below) (Criegee, *Liebigs Ann. Chem.*, 1936, *522*, 75). *cis*-Dihydroxylation of olefins with potassium permanganate in alkaline media has been known for quite some time (Robinson and Robinson, *J. Chem. Soc.*, 1925, *127*, 1628), and this reaction appears to proceed through a cyclic ester **VI**. Thus attempts at permanganate dihydroxylation have been performed.




**V**




**VI**

Previous reports have indicated that permanganate dihydroxylation of olefins in acid or neutral conditions causes over-oxidation of the initial diol products with concomitant production of ketones and carboxylates. Only in alkaline conditions further oxidation of the diol products can be decelerated. As **41** is a carboxylic ester the reaction cannot be done in aqueous alkali. Hazra *et al.* (J. Chem. Soc. Perkin Trans. I, 1994, 1667) describes successful dihydroxylation of highly substituted olefins to the corresponding diols using tetradecyltrimethylammonium permanganate (TDTAP) in a mixture of *t*-BuOH, dichloromethane and water in the presence of 0.1 equivalent of KOH. Application of this method to dihydroxylation of **41** results in rapid formation (within 10 minutes at room temperature) of a mixture of **42** and its diastereomer in an 8:1 ratio, which is isolated in 71% yield. Oxidation occurs much faster in similar reactions without KOH, but the yield of **42** is not improved.

Mukaiyama et al. (Chem. Lett., 1983, 173) disclosed dihydroxylation of olefins with $KMnO_4$ and 18-crown-6 ether in dichloromethane at –40°C. Attempts at dihydroxylation of **41** under Mukaiyama's conditions but at different temperatures

offer a 6:1 mixture of **42** and its diastereomer in 50% yield at –40°C and the same mixture in 94% yield at –10°C.

Surprisingly, in contrast to the teaching of the prior of art which discloses that oxidation of a double bond with $KMnO_4$ proceeds via diol wherein the resultant diol is rapidly oxidized further without the presence of base, diol **42** was found to be isolable when the corresponding **41** is treated with $KMnO_4$ without added alkali and crown ether. In pure *t*-butanol, oxidation does not proceed even at room temperature conditions for two days. Addition of water to the mixture promotes the reaction. It is found that the more water in the reaction media the faster the reaction proceeds with poor selectivity of **42** production; the less water the slower the reaction but improved selectivity. In any case, the yield is rather poor due to further oxidation.

Most surprisingly, and in contradiction to the prior art, treatment of **41** with $KMnO_4$ in acetone is found to give a 10:1 mixture in quantitative yield, the desired **42** being the major component. The stereoselectivity is found to be improved by performing the reaction in a mixture of acetone and pyridine.

The following Examples are set forth to aid in an understanding of the invention. This section is not intended to, and should not be interpreted to, limit in any way the invention set forth in the claims which follow thereafter.

## EXAMPLES

### EXAMPLE 1

*(2S, 3R, 4R)-4,5-O-isopropylidene-2,3-O-sulfuryl-2,3,4,5-tetrahydroxy-2-methyl-pentanoic acid ethyl ester (IIIb, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$)*

To a solution of (2S, 3R, 4R)-4,5-O-isopropylidene-2, 3, 4, 5-tetrahydroxy-2-methyl-pentanoic acid ethyl ester ($R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$) (2.0 g, 8.06 mmol) in anhydrous methylene chloride (40 mL) containing triethyl amine (3.4 mL) was added at 0°C thionyl chloride (0.88 mL, 12.08 mmol) dropwise over 10 min. The resulting reaction mixture was stirred at 0°C for 10 min, diluted with cold ether (100 mL), washed with water (50 mL x 2) and brine (50 mL x 2), dried with sodium sulfate, and concentrated to give a residue (IIIa, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$) which was dissolved in acetonitrile-tetrachloromethane (10: 10 mL). To the obtained solution was added at room temperature sodium periodate (2.58 g, 12.06 mmol),

ruthenium trichloride (16 mg, 0.077 mmol), and water (14 mL) subsequently. The resulting reaction mixture was stirred at room temperature for 10 min, diluted ether (100 mL), washed with water (50 mL x 2), saturated sodium bicarbonate solution (50 mL x 2), and brine (50 mL x 2), dried with sodium sulfate, concentrated, and co-evaporated with toluene (30 mL x 3) to a syrupy residue, the sulfate **IIIb** (2.23 g, 89%) which was used for the next reaction without further purification. $^1$H NMR ($CDCl_3$) δ (ppm) 5.04 (d, 1H, J = 9.6 Hz, H-3), 4.37 (m, 1H, H-4), 4.29 (q, 2H, J = 7.6 Hz, $C\underline{H}_2CH_3$), 4.17 (dd, 1H, J = 5.6, 9.6 Hz, H-5), 4.05 (dd, 1H, J = 3.2, 9.6 Hz, H-5'), 1.8 (s, 3H,$CH_3$-2), 1.38 (s, 3H, $(C\underline{H}_3)_2C$), 1.32 (t, 3H, J = 6.8Hz, $CH_2C\underline{H}_3$), 1.31 (s, 3H, $(C\underline{H}_3)_2C$).

EXAMPLE 2

*Tetrabutylammonium salt of (2R, 3S, 4R)-2-fluoro-4,5-O-isopropylidene-2-methyl-3-sulfooxy-3,4,5-trihydroxypentanoic acid ethyl ester (51B, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$, Nu = F, $M^+$ = tetrabutylammonium)*

Method 1: To a solution of the sulfate IIIb from Example 1 (628 mg, 2.02 mmol) in anhydrous tetrahydrofuran was added at 0°C tetrabutylammonium fluoride (1M in tetrahydrofuran, dried with 4Å molecular sieves) dropwise over 5 min. The resulting reaction mixture was stirred at 0°C for 20 min, another 2 m L of tetrabutylammonium fluoride (1M in tetrahydrofuran, dried with 4Å molecular sieves, 3 mL) was added, and then the reaction mixture was stirred at 0°C for 2 hours, then concentrated, and purified by silica gel column chromatography (EtOAc) to give to the fluorinated sulfate, as a syrup (350 mg, 38%). $^1$H NMR ($CDCl_3$) δ (ppm) 4.66 (dd, 1H, J = 9.6, 25.6 Hz, H-3), 4.48 (dd, 1H, J = 5.2, 8.8 Hz, H-4), 4.20, 4.07 (2m, 4H, H-5, $OC\underline{H}_2CH_3$), 3.21 (m, 8H, $N(C\underline{H}_2CH_2CH_2CH_3)_4$), 1.69 (d, 3H, J = 22.4 Hz, $CH_3$-2), 1.59 (m, 8H, $N(CH_2C\underline{H}_2CH_2CH_3)_4$), 1.39 (m, 8H, $CH_2CH_2C\underline{H}_2CH_3)_4$), 1.27-1.25 (m, 9H, $OCH_2C\underline{H}_3$, $(C\underline{H}_3)_2C$), 0.96 (t, 12H, J = 6.8 Hz, $CH_2CH_2CH_2C\underline{H}_3)_4$.

Method 2: To a solution of the cyclic sulfate **IIIb** (480 mg, 1.55 mmol) in anhydrous tetrahydrofuran was added at 0°C tetrabutylammonium fluoride (1M in tetrahydrofuran, neutralized with HF-pyridine, 3.1 mL) dropwise over 5 min. The resulting reaction mixture was stirred for 39 hours, concentrated, and purified by

silica gel column chromatography ($CH_2Cl_2$:MeOH = 10:1) to the fluorinated sulfate as a syrup (280 mg, 39%).

EXAMPLE 3

*2-Deoxy-2-fluoro-2-C-methyl-D-ribono-γ-latone (53B, $R^2$ = H, $R^3$ = $CH_3$, Nu = F)*

A mixture of the product of Example 2(170 mg, 0.370 mmol), trifluoroacetic acid (0.8 mL), and water (2 mL) in acetonitrile (10 mL) was heated at 80 °C for 1.5 hours, diluted with ethyl acetate (15 mL), washed with water (10 mL) and saturated sodium bicarbonate solution (10 mL). The aqueous layer was saturated with NaCl and extracted with ethyl acetate (10 mL). The combined organic layer was dried with sodium sulfate, filtered, and concentrated to give a residue, which was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1 to $CH_2Cl_2$:MeOH = 20:1) to give the desired compound as a white solid (60 mg, 100%). $^1$H NMR ($CDCl_3$) δ (ppm) 6.06 (d, 1H, J = 6.8 Hz, HO-3), 5.16 (t, 1H, J = 4.8 Hz, HO-5), 4.26 (m, 1H, H-4), 3.98 (ddd, 1H, J = 7.2, 8.0, 23.2 Hz, H-3), 3.78 (ddd, 1H, J = 2.0, 5.2, 12.8 Hz, H-5), 3.55 (ddd, 1H, J = 4.4, 5.6, 12.4 Hz, H-5'), 1.48 (d, 3H, J = 24 Hz, $CH_3$-2); $^{13}$C NMR ($CDCl_3$) δ (ppm) 171.2 (d, J = 21.2 Hz, C-1), 92.5 (d, J = 177.5 Hz, C-2), 83.37 (C-4), 70.2 (d, J = 15.9 Hz, C-3), 59.0 (C-5), 17.1 (d, J = 25.0 Hz, $\underline{C}H_3$-C-2).

EXAMPLE 4

*3,5-Di-O-benzoyl-2-deoxy-2-fluoro-2-C-methyl-D-ribono-γ-latone (49B, $R^2$ = H, $R^3$ = $CH_3$, $R^5$ = Bz, $R^6$ = Bz, Nu = F)*

The compound of Example 3 (60 mg, 0.16 mmol) was dissolved in anhydrous pyridine (1 mL) and enzoyl chloride (0.3 mL) was added. The resulting reaction mixture was stirred at room temperature for 20 min, water added (1 mL), stirred for 20 min, diluted with ethyl acetate (5 mL), washed with water (2 mL) and 1M HCl (2 mL x 3), and dried with sodium sulfate. Upon filtration and concentration, the residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 10:1) to give 3,5-di-O-benzoyl-2-deoxy-2-fluoro-D-ribono-γ-latone as a white solid (118 mg, 87%). $^1$H NMR ($CDCl_3$) δ (ppm) 8.08 (m, 2H, aromatic), 7.99 (m, 2H, aromatic), 7.63 (m, 1H, aromatic), 7.58 (m, 1H, aromatic), 7.49 (m, 2H, aromatic), 7.43 (m, 2H, aromatic), 5.51 (dd, 1H, J = 7.2, 17.6 Hz, H-3),

5.00 (m, 1H, H-4), 4.78 (dd, 1H, J = 3.6, 12.8 Hz, H-5), 4.59 (dd, 1H, J = 5.2, 12.8 Hz, H-5'), 1.75 (d, 3H, J = 23.6 Hz, $CH_3$-2)

EXAMPLE 5

*Tetraethylammonium salt of (2R, 3S, 4R)-4,5-dihydroxy-2-fluoro-4,5-O-isopropylidene-2-methyl-3-sulfooxy-pentanoic acid ethyl ester (51B, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$, Nu = F, $M^+$ = tetraethylammonium)*

Method 1. To a solution of the sulfate **IIIb** (Scheme 9) (1.96 g, 6.32 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was added at 0 °C tetraethylammonium fluoride hydrate (1.39 g, 9.13 mmol) in one portion. The resulting reaction mixture was stirred for 30 min, concentrated, and co-evaporated with toluene to give a semi-solid (**51b**) (3.35g, crude, proton NMR showed virtually one product). $^1$H NMR ($CDCl_3$) δ (ppm) 4.61 (dd, 1H, J = 9.2, 25.6 Hz, H-3), 4.51 (dd, 1H, J = 5.2, 9.2 Hz, H-4), 4.23-4.05 (m, 4H, H-5, $OC\underline{H}_2CH_3$), 3.32 (q, 8H, J = 7.2 Hz, $N(C\underline{H}_2CH_3)_4$), 1.69 (d, 3H, J = 23. 2 Hz, $CH_3$-2), 1.31-1.24 (m, 21H, $OCH_2C\underline{H}_3$, $(C\underline{H}_3)_2C$, $N(CH_2C\underline{H}_3)_4$.

Method 2: To a solution of the sulfate IIIb (148 mg, 0.477 mmol) in anhydrous acetonitrile (2 mL) was added at 0 °C tetraethylammonium fluoride hydrate (107 mg, 0.717 mmol) in one portion. The resulting reaction mixture was stirred for 24 hours, concentrated, and co-evaporated with toluene to give a semi-solid (257 mg, crude, proton NMR showed virtually one product).

EXAMPLE 6

*Preparation of 1-(2-deoxy-2-fluoro-2-methyl-3,5-O-3,5-dipivaloyl-ribofuranosyl)-$N^4$-benzoylcytosine (11b, $R^5$=$R^6$=pivaloyl, $R^2$=H, $R^3$=Me)*

To a solution of **49B**, (Scheme 6) (Nu=F, $R^2$=H, $R^3$=Me, $R^5$=$R^6$=pivaloyl, 3.44g, 10.36 mmol) in THF (70 mL) was added LiAl(*t*-BuO)$_3$H (13.47 mmol, 1M in THF, 13.47 mL) at –20 °C to –10 °C and the resulting solution was stirred at –10°C to –15°C for 2 h. To the solution was added an additional LiAl (*t*-BuO)$_3$H (1.35 mL, 1.35 mmol) and the solution was stirred at –10 C for 1h. Ice water (50 mL) was added. The mixture was extracted with EtOAc (200 mL), and the organic layer was washed with water, brine and dried ($Na_2SO_4$). Solvent was removed to give crude

lactol which was dissolved in $CH_2Cl_2$ (50 mL). To the solution were added $Et_3N$ (31.08 mmol, 4.24 mL), 4-dimethylaminopyridine (1 mmol, 122mg) and trimethylacetyl chloride (20.7 mmol, 2.55 mL), and the mixture was stirred at room temperature for 16 h. Water (20 mL) was added, and the resulting mixture was stirred at room temperature for 10 min. EtOAc (200 mL) was added, and organic solution was washed with water, brine, and dried ($Na_2SO_4$). Solvent was removed and the residue was co-evaporated with toluene (2x20 mL) to give a crude intermediate (**5**, 6.74g) for the next coupling reaction without purification.

A suspension of $N^4$-benzoylcytosine (6.06 mmol, 1.30 g) and $(NH_4)_2SO_4$ (30 mmg) in HMDS (16.7 mL) was refluxed for 5 h, and the clear solution was concentrated to dryness under reduced pressure. The residue was dissolved in 1,2-dichloroethane (50 mL). To the solution were added crude **54** (1.96 g, Scheme 6) and $SnCl_4$ (1.42 mL, 12.12 mmol) at room temperature. The solution was refluxed for 24 h. and cooled to 0 °C. To the solution were added $NaHCO_3$ (6.11g, 72.72 mmol) and EtOAc (50 mL). To the mixture was added $H_2O$ (2 mL) slowly, and the resulting mixture was stirred at room temperature for 20 min. Solid was removed by filtration. The organic solution was washed with water, brine and dried ($Na_2SO_4$). Solvent was removed to give syrup as crude mixture of β/α-anomers with a ratio of 4/1 in favor to β-isomer. The crude product was dissolved in MeOH (1 mL) at 50 °C. To the solution was added hexanes (10 mL). The mixture was allowed to stay at room temperature for 1h, then 0 °C for 2 h. Crystals were collected by filtration, washed with hexanes to give product **55**, Scheme 6 (323 mg, 20.3% from **49**). Mother liquor was concentrated to dryness and purified by column chromatography (20-50% EtOAc in hexanes) to give second crop of **55**. H-NMR ($CDCl_3$): δ 8.82 (br s, 1H, NH), 8.10, 7.89, 7.62, 7.52 (m, 7H, H-5, H-6, 5Ph-H), 6.41 (d, J = 18.4Hz, 1H, H-1'), 5.10 (m, 1H, H-3'), 4.45 (d, J = 9.6Hz, 1H, H-4'), 4.36 (t, J = 2.8Hz, 2H, H-5'), 1.35 (d, J = 22.0Hz, 3H, Me), 1.29, 1.23 [ss, 18H, $C(Me)_3$].

EXAMPLE 7

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*4-Methylmorpholine N-oxide as oxidant with Osmium catalyst.*

To a stirred solution of compound **41** (214 mg, 0.1 mmol) in *t*-BuOH under argon was added a solution of 4-methylmorpholine N-oxide (0.47 mL, 50 wt % solution in $H_2O$) and water (0.2 mL). A 2.5 wt% solution of osmium tetraoxide in *tert*-butyl alcohol (0.51 mL) is added, and the mixture is stirred for 5 h at room temperature in a water bath. The mixture is evaporated *in vacuo* to a syrup, which is azeotroped with $H_2O$ (3 x 10 mL) to remove 4-methylmorpholine. The residue is dried by addition and evaporation of EtOH (2 x 10 mL) to give a residue, which was purified by silica gel column chromatography with 20 % EtOAc in hexanes to provide the desired product and its isomer (196 mg, 79%) as a solid. Proton NMR indicates that the ratio of the desired product to its isomer is around 5:1. Recrystallization of the mixture from hexanes/ethyl acetate gives pure product (91 mg, 37.4% from starting material) as a crystalline solid. $^1$H NMR (DMSO-$d_6$) δ 1.18 (t, $J$ = 7.2 Hz, 3H, -$OCH_2\underline{CH_3}$), 1.24 (s, 3H, $CH_3$), 1.25 (s, 3H, $CH_3$), 1.28 (s, 3H, 2-$CH_3$), 3.67 (t, $J$ = 7.2 Hz, 1 H), 3.85, 4.06 and 4.12 (m, 4 H), 4.97 (s, 1H, 2-OH, $D_2O$ exchangeable), 5.14 (d, $J$ = 7.6 Hz, 2-OH, $D_2O$ exchangeable).

EXAMPLE 8

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium ferricyanide as oxidant with Osmium catalyst.*

A 100 mL round-bottomed flask, equipped with a magnetic stirrer, is charged with 5 mL of *tert*-butyl alcohol, 5 mL of water, and a mixture of $K_3Fe(CN)_6$ (0.98 g), $K_2CO_3$ (0.41 g), and $K_2OsO_2(OH)_4$ (3.2 mg). Stirring at room temperature produced two clear phases; the lower aqueous phase appears bright yellow. Methanesulfonamide (95 mg) is added at this point. The mixture is cooled to 0 °C whereupon some of salts precipitate out, 214 mg (1 mmol) of the compound **41** is added at once, and the heterogeneous slurry is stirred vigorously at 0 °C for 24 h. To the mixture is added solid sodium sulfite (1.5 g) while stirring at 0 °C, and then the mixture is allowed to warm to room temperature and stirred for 30-60 min. Ethyl acetate (10 mL) is added, and after separation of the layers, the aqueous phase is further extracted with EtOAc. The organic layer is dried over $Na_2SO_4$ and concentrated to dryness. The residue is purified by silica gel column chromatography with 20 % EtOAc in hexanes to provide the product (190 mg, 77%) as a solid. proton NMR indicates that the ratio of the desired product to its isomer is around 5:1. Recrystallization of the mixture with hexanes/ethyl acetate gave pure diol product (102 mg, 41% from starting material) as a crystalline solid. The $^1H$ NMR spectrum of this product is identical to that of an authentic specimen.

EXAMPLE 9

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*t-Butylhydroperoxide as oxidant at room temperature with Osmium catalyst.*

A 50 mL of flask, equipped with magnetic stirrer, is charged with 2 mL of acetone, 214 mg (1 mmol) of compound **41**, 65 mg of $Et_4NOAc \cdot 4H_2O$, and 0.3 mL of *tert*-butyl hydroperoxide (5 ~ 6 M in decane). After stirring at room temperature until the $Et_4NOAc$ a clear solution is obtained, the resulting solution is cooled in an ice bath and 5 mL of $OsO_4$ (2.5 wt% in t-BuOH) is added in one portion. The

solution immediately becomes brownish purple. After 1 h the ice bath is removed and the reaction mixture is allowed to warm to room temperature and stirred for 14 h. The rest of the procedure is done exactly the same way as described above. After flash column chromatography, 178 mg (72%) of product is obtained as a solid. In an expanded $^1$H NMR, a tiny bump is observed at δ 1.26 indicating the presence of an isomer in less than 4% in the product.

EXAMPLE 10

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*t-Butylhydroperoxide as oxidant at 0 °C with Osmium catalyst.*

A 250 mL of flask, equipped with magnetic stirrer, is charged with 20 mL of acetone, 2.14 g (10 mmol) of compound 41, 650 mg of $Et_4NOAc•4H_2O$, and 3 mL of *tert*-butyl hydroperoxide (5 ~ 6 M in decane). After stirring at room temperature until the $Et_4NOAc$ has dissolved, the resulting solution is cooled in an ice bath and 5 mL of $OsO_4$ (2.5 wt% in *t*-BuOH) is added in one portion. The solution immediately becomes brownish purple. The reaction mixture is then stirred at 0 °C for 6.5 h (monitored by TLC, hexanes: ethyl acetate = 4:1, Rf = 0.18). Ether (40 mL) is added at 0 °C and the resulting mixture is treated with 5 mL of freshly prepared 10 % $NaHSO_3$ solution in one portion. The ice bath is removed and stirring is continued for 1 h. EtOAc (100 mL) and $H_2O$ (50 mL) are added to the mixture. After separation of the layers, the aqueous phase is further extracted with EtOAc. The organic layer is washed with brine, dried ($MgSO_4$) and concentrated. The residue is purified by a flash silica gel column chromatography with 20 % EtOAc in hexanes to provide the product (2.16 g, 87%) as a solid. No contamination of an isomer is detected in this product by vigorous $^1$H NMR analyses.

EXAMPLE 11

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Tetradecyltimethylammonium Permanganate(TDTAP) as Oxidant.*

To a stirred solution of compound **41** (214 mg, 1 mmol), in *t*-BuOH (10 mL) and $CH_2Cl_2$ (2 mL) at room temperature is added a solution of KOH (6 mg, 0.1 mmol) in water followed by TDTAP (0.420 g, 1.12 mmol) in small portions over a period of five minutes. TLC after 5 minutes showed that the reaction is complete. The solution is quenched by using 10 mL of saturated sodium bisulfite. The reaction mixture is concentrated in vacuo and the residue extracted with ethyl acetate (3 x 15 mL), dried ($Na_2SO_4$), evaporated to give a white solid, which is further dissolved in 5 mL of $CH_2Cl_2$, passed it through a plug of silica gel topped with Celite, washed with ethyl acetate (50 ml). The filtrate is dried in vacuo to give viscous oil (174 mg 71% yield) as an 8:1 mixture of which the predominant isomer is the titled compound.

EXAMPLE 12

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant with 18-Crown-6 ether – A (at –40 °C).*

To a solution of compound **41** (214 mg, 1 mmol) in $CH_2Cl_2$ (10 mL) and 18-crown-6-ether (37.5 mg, 0.1 mmol) is added $KMnO_4$ (158 mg, 1 mmol) in portions at –40°C, and the mixture stirred for 2 h at the same temperature. During this time the reaction mixture turns to dark brown. After the reaction was complete, mixture is quenched with saturated solution of sodium bisulfite (10 mL). The resulting colorless mixture is filtered through a frit, and extracted the filtrate with ethyl acetate (2 x 25 ml), dried ($Na_2SO_4$) and concentrated to give a viscous oil consisting of 10-20% of unreacted olefin starting material along with the desired diols and its isomer in a ratio of 6:1 ($^1$H NMR). Olefin starting material can be removed by passing through a small pad of silica gel using 5% ethyl acetate: hexane. A 6:1 mixture of

the desired diols is eluted from the column with 20% ethyl acetate/hexane, and obtained as a white solid (200 mg ~80%) upon evaporation of the solvent.

EXAMPLE 13

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant with 18-Crown-6 ether – B (at –10 °C).*

To a solution of compound **41** (214 mg, 1 mmol) in $CH_2Cl_2$ (10 ml) is added 37.5 mg (0.1 mmol) of 18-crown-6-ether, and mixture is cooled to –10 °C. $KMnO_4$ (237 mg, 1.5 mmol) is added in portions, and the mixture stirred at –10 °C for 2 h. During this time the reaction mixture turns to dark brown, which is treated with saturated solution of sodium bisulfite (10 mL). The resulting mixture is filtered through a frit, and the filtrate is extracted with ethyl acetate (2 x 25 ml), dried ($Na_2SO_4$) and evaporated to give a white solid (240 mg, 94.4%) consisting of the desired product and its isomer in a ratio of 6:1.

EXAMPLE 14

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant in 1:9 $H_2O$/t-BuOH.*

To a solution of compound **41** (214 mg, 1 mmol) in *t*-BuOH (9 mL) and $H_2O$ (1 mL) at 0 °C is added $KMnO_4$ (237 mg, 1.5 mmol) in portions and the mixture stirred at the same temperature for 2h. An additional amount (79 mg, 0.5 mmol) of $KMnO_4$ is charged and the mixture is stirred for another 30 minutes. After work up as above, 128 mg (50%) of a mixture of isomers in a ratio of 8:1 is obtained as a white solid in which the major component is the desiredproduct.

EXAMPLE 15

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant in 9:1 $H_2O$/t-BuOH.*

To a solution of compound **41** (214 mg, 1 mmol) in $H_2O$ (9 mL) and t-BuOH (1 mL) at 0 °C is added $KMnO_4$ (237 mg, 1.5 mmol) in portions and stirred at the same temperature for 30 minutes. During this time the mixture turns to dark brown. Saturated solution of sodium bisulfite (10 mL) is added to the mixture, which is filtered, and the filtrate is extracted with ethyl acetate (3x25 ml), dried ($Na_2SO_4$), and concentrated to give a 4:1 mixture of diol isomers as a white solid (128 mg, 50%), in which the titled compound is the major component.

EXAMPLE 16

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant in $H_2O$ at 0 °C.*

A solution of $KMnO_4$ (158 mg, 1.0 mmol) in $H_2O$ (10 mL) is added to compound **41** (214 mg, 1 mmol), and the mixture is stirred at 0 °C for 1 hour. The reaction mixture is quenched with saturated solution of sodium bisulfite (10 mL), and the mixture is worked up as above. A white solid (80 mg, 32%) that is obtained is a 4:1 mixture of diol isomers in which the titled compound is the predominant component.

EXAMPLE 17

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant in Acetone.*

To a solution of compound **41** (214 mg, 1 mmol) in acetone (10 mL) is added 37.5 mg, 0.1 mmol) and cooled the reaction mixture to 0° C. To this cold solution is added $KMnO_4$ (237 mg, 1.5 mmol) in portions, and the reaction mixture is stirred for 2 h at the same temperature. During this time the reaction mixture turns to dark brown. The reaction mixture is quenched with saturated solution of sodium bisulfite

(10 ml) where the solution becomes colorless. The reaction mixture is extracted with ethyl acetate (3 x 25 ml), dried and evaporated the mixture to give a white solid (245 mg, 96.4%) in the ratio of 10:1.

EXAMPLE 18

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42)*

*Potassium Permanganate as Oxidant in a mixture of Acetone and Pyridine.*

To a solution of compound **41** (214 mg, 1 mmol) in a mixture of acetone (9 mL) and pyridine (1 mL) at 0 °C is added $KMnO_4$ (158 mg, 1.0 mmol) and stirred at same temperature for 1 hr. After work up of the reaction mixture as above, 164 mg (67%) of white solid which is practically pure product. Vigorous $^1H$ NMR analyses reveal the crude white solid contains about 6% of the diastere-omer of the titled compound.

EXAMPLE 19

*(2S, 3R)-3-[(4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl]-2,3-dihydroxy-2-methyl-propionic acid ethyl ester (42) in the $RuCl_3/CeCl_3/NaIO_4$ system*

In a 50 mL round-bottomed flask equipped with magnetic stirring bar, a mixture of $NaIO_4$ (321 mg, 1.5 mmol) and $CeCl_3 . 7H_2O$ (37 mg, 0.1 mmol) in 0.45 mL of water is stirred and gently heated until a bright yellow suspension is formed. After cooling to 0 °C, EtOAc (1.25 mL) and acetonitrile (1.5 mL) are added and the suspension is stirred for 2 minutes. A 0.1 M aqueous solution of $RuCl_3$ (25 µL) is added and the mixture is stirred for 2 minutes. A solution of the compound **41**, (214 mg, 1 mmol) in EtOAc (0.25 mL) is added in one portion and the resulting slurry is stirred at 0 °C for 1 hour. Solid $Na_2SO_4$ (0.5 g) is added followed by EtOAc ( 3 mL). The solid is filtered off, and the filter cake is washed several times with EtOAc. Then the filtrate is washed with saturated $Na_2SO_3$ solution and the organic layer is dried ($Na_2SO_4$) and concentrated to dryness. The residue is purified by silica gel column chromatography with 20 % EtOAc in hexanes to provide a syrup (150 mg, 60%). $^1H$ NMR indicates that the ratio of the desired product to its isomer is approximately 1.6:1.

EXAMPLE 20

*Reduction and Acylation of compound 49*

To a solution of 3,5-dibenzoyl-2-fluoro-2-deoxy-2-methyl-D-ribono-lactone (49, 23g, 61.77 mmol, scheme 6 ) in anhydrous THF (400 ml) was added LiAl($^t$-OBu)$_3$H (75 mL 1M in THF, 75.0 mmol) over a period of 15 min at -20 to -10 oC and the resulting solution was stirred at the same temperature until all the starting material was consumed. After 5 hours, ~10-20% starting material was left, therefore additional 10 mL of LiAl(*t*-OBu)$_3$H (10 mmol) was added at the same temperature and stirred for an hour when TLC indicated all starting material was consumed. To this reaction mixture were added DMAP (7.5 g) and $Ac_2O$ (58.2 g, 616 mmol) and the solution was stirred at –10 °C for ~2-3 h. Upon completion of reaction (as indicated by TLC) the reaction mixture was diluted with ethyl acetate (400 ml) and 200 ml of water. The organic layer was separated and the aqueous layer was washed with ethyl acetate (2X100 ml). The combined organic layer was washed with water (3x150 ml), brine and dried over anhy. $Na_2SO_4$. The solvent was removed under reduced pressure and coevaporated with toluene (2X100 mL) to give crude acetate as a clear brown oil. This oil was passed through a plug of silica gel (50 g) and washed with 20% ethyl acetate/hexanes until all the acetate was recovered. The solvent was evaporated under reduced pressure to give the desired acetate (**54**, 32g) as a colorless oil.

EXAMPLE 21

*1-(2-deoxy-2-fluoro-2-methyl-3-5-O-dibenzoyl-β–D-ribofuranosyl)-N4-benzoylcytosine (55)*

To a suspension of $N^4$-benzoylcytosine (20.39 g, 94.74 mmol) in 400 ml of HMDS was added $(NH_4)_2SO_4$ (250 mg) and heated under reflux for 4h. Excess HMDS was removed under reduced pressure. The oily residue was dissolved in chlorobenzene (1L). To this solution were added a solution of the acetate (25 g) in chlorobenzene (250 mL) and $SnCl_4$ (190.4 mmol, 49 g) and the mixture was stirred at room temperature for 2 h followed by heating at ~65 °C for 16 h. The reaction mixture was cooled to 0°C to which $NaHCO_3$ (96 g, 1.14 mol) and ethyl acetate (500 ml) were added followed by careful addition of water (20 ml). This mixture was allowed to stir at room temperature for 30 min. The mixture was filtered under

vacuum, the residue washed with ethyl acetate. The organic layer was washed with water, brine (2 X 250 mL) and dried over anhydrous $Na_2SO_4$. Solvent was removed under reduced pressure to give a pale yellowish-brown solid. This was dissolved in MeOH (250 mL) heated under reflux for 30 minutes, cooled to room temperature and filtered, to give the desired product (**55**, 8.0 g) as a off-white solid.

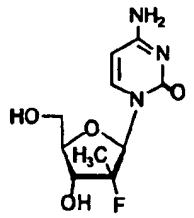
EXAMPLE 22

*1-(2-deoxy-2-fluoro-2-C-methyl-β-D-ribofuranosyl)cytosine (14)*

A suspension of **55** from Example 21 (16.7 g, 30.8 mmol, scheme 6) was treated with methanolic ammonia (750 mL, 7M in MeOH) and stirred at room temperature for 12 h and concentrated to dryness under reduced pressure to give pale yellow solid. THF (400 mL) was added to the solid and heated under reflux for 30 minutes and cooled to room temperature. The solid formed was collected by filtration and washed with THF to give **14** (6.7 g, 88%) as an off-white powder.

WE CLAIM:

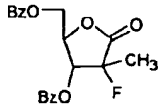
1. A method of synthesizing a 2'-deoxy-2'-fluoro-2'-C-methyl-β-D-ribofuranosyl nucleoside of the following formula:



14

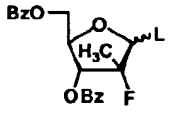
comprising the following steps:

(a) reducing the lactone of formula 49,



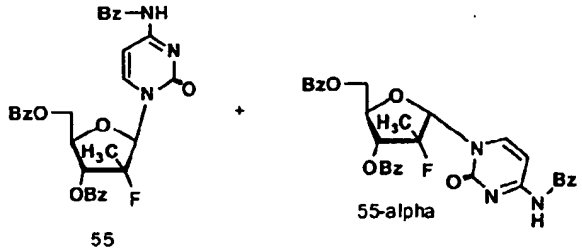
49

to the corresponding sugar followed by acetylation to yield the compound of formula 54B; wherein L is any leaving group;



54B

(b) condensation of the product of step (a), 54B, in a catalyst, with a silylated base to produce a mixture of protected nucleosides, 55 and55-α;



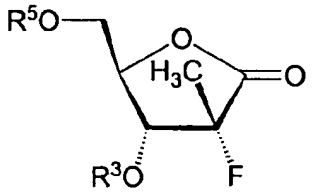
55 55-alpha

(c) separation of the anomers of step (b), 55 and 55-alpha; and

(d) deprotection of the protected nucleoside of step (c), 55, to produce the desired nucleoside.

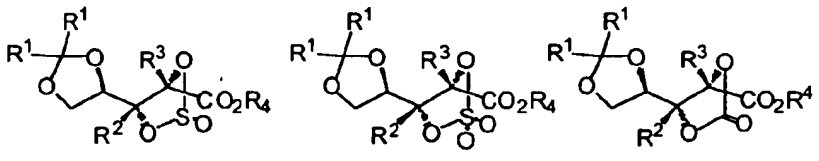
2. The method of claim 1, wherein the silylated base of step (b) is silylated $N^4$-benzoylcytosine andis deprotected with a metal alcoholate in alcohol.

3. A 3,5-di-O-protected-2-deoxy-2-fluoro-2-C-methyl-D-ribono-γ-lactone of the following general formula:



wherein $R^3$ and $R^5$ can be independently H, $CH_3$, acetyl, benzoyl, pivaloyl, or 4-nitrobenzoyl, 3-nitrobenzoyl, 2-nitrobenzoyl, 4-chlorobenzoyl, 3-chlorobenzoyl, 2-chlorobenzoyl, 4-methylbenzoyl, 3-methylbenzoyl, 2-methylbenzoyl, para-phenylbenzoyl, and other optionally substituted acyl ($R^3$ and $R^5$ are –C(O)-R, R can be independently lower alkyl of $C_1$-$C_6$, , or aryl of $C_7$-$C_{20}$), benzyl, 4-methoxybenzyl and other optionally substituted benzyl ($R^3$ and $R^5$ can be independently aryl of $C_7$-$C_{20}$), trityl, trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups; or alternatively, $R^{3'}$ and $R^{5'}$ are linked through -$SiR_2$-O-$SiR_2$- or -$SiR_2$-, wherein R is a lower alkyl such as $CH_3$, ethyl, and n-Pr or I-Pr.

4. The cyclic sulfite (**IIIa**), cyclic sulfate (**IIIb**), and cyclic carbonate (**IIIc**) of the following general formula:



**IIIa** **IIIb** **IIIc**

wherein

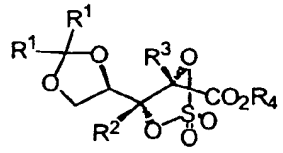
$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl;

alternatively, $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively;

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and

$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including, benzyl, lower alkyl including methyl, ethyl, or propyl.

5. The cyclic sulfate **(IIIb)** of the following general formula:



**IIIb**

wherein

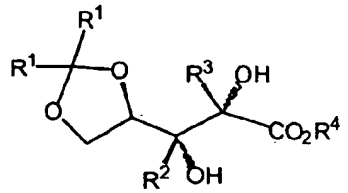
$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl;

alternatively, $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively;

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-), and

$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including, benzyl, lower alkyl ($C_{6\text{-}10}$) including methyl, ethyl, or propyl.

6. A process for the preparation of a compound of formula IIIa of claim 4, comprising reacting a compound of formula, 42B,



42B

with a thionyl compound in presence of a base, wherein the base is a trialkylamine, in a solvent.

7. The process of claim 6, wherein the thionyl compound is thionyl chloride or thionyl diimidazole.

8. The process of claim 6, wherein the trialkylamine is selected from the group consisting of triethylamine, diisopropyl ethylamine and pyridine.

9. A process for preparation of a compound of formula IIIb of claim 5, comprising:

(a) mixing compound **IIIa** of claim 4 with one or more oxidants in one or more solvents;

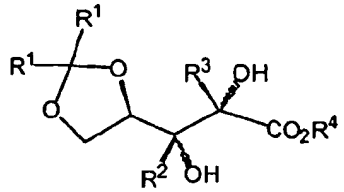
(b) alternatively, mixing a compound of the formula, **42B** of claim 6, with

sulfuryl chloride or sulfuryl diimidazole in presence of a base, in a solvent.

10. The process of claim 9, wherein the base is selected from one or more of the group consisting of trialkyl amine including triethylamine, diisopropyl ethylamine, and pyridine.

11. The process of claim 6, wherein the solvent is selected from one or more of the group consisting of chloroform, methylene chloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, benzene, toluene, and water.

12. A process for the preparation of a compound of formula, IIIc of claim 5,



42B

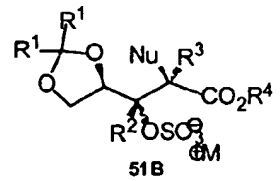
comprising mixing a compound of the formula, 42B, with carbonyl diimidazole in presence of a base, in solvent, or alternatively, with dimethyl carbonate at an elevated temperature.

13. The method of claim 9, wherein the oxidant is selected from one or more of the group consisting of $RuCl_3$, $KMnO_4$, TEMPO, $NaIO_4$, $KIO_4$, $HIO_4$, mCPBA, NaOCl, and oxone.

14. The process of claim 12, wherein the base is a trialkyl amine or pyridine.

15. The process of claim 12, wherein the solvent is selected from one or more of the group consisting of: chloroform, methylene chloride, 1,2-dichloroethane, diethyl ether, and tetrahydrofuran.

16. A compound of the following general formula 51B:



51B

wherein,

$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl; alternatively, $R^1$ is a part of

cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl, respectively; $R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

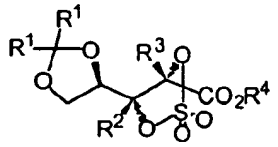
$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including benzyl, lower alkyl ($C_{6\text{-}10}$) including methyl, ethyl, propyl;

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or NR where R is acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl including methyl, ethyl, or propyl; and

$M^+$ is tetraalkylammonium including tetrabutylammonium, tetraethylammonium, tetramethylammonium, or metal cation including sodium, potassium, cesium, rubidium, and silver cations.

17. A process for the preparation of compounds of the general formula **51B** of claim 16, comprising:

mixing a compound of the following formula, IIIb



IIIb

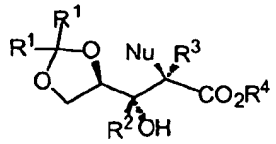
with at least one fluoride source and a phase transfer catalyst in an appropriate solvent,

with $NaBH_4$, tetraalkylammonium chloride, tetraalkylammonium bromide, $NaN_3$ or $LiN_3$,$NH_4SCN$, $CF_3I$-tetrakis(dimethylamino)-ethylene (TDAE), tetraalkylammonium nitrate, KCN, $NH_4OR$, HNR where R is lower alkyl or acyl, $LiCu(R)_2$ where R is methyl, ethyl, ethylenyl, or ethnyl.

18. The method of claim 17, wherein the fluoride source is selected from the group consisting of tetramethylammonium fluoride (TMAF), tetraethylammonium fluoride (TEAF), tetrabutylammonium fluoride (TBAF),tris(dimehtylamino)sulfur (trimethylsilyl)difluoride (TAS-F), silver fluroide (AgF), potassium fluoride (KF), cesium fluoride (CsF), and rubidium fluoride (RbF).

19. The method of claim 17, wherein the solvent is selected from one or more of the group consisting of *N,N*-dimethylformamide, tetrahydrofuran, acetone, diethyl ether, diglyme, polyethylene glycol, DMSO, MeCN, and dioxane.

20. A compound of the following general formula **52B**:




**52B**

wherein,

$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl; or $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-);

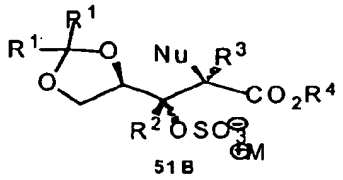
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including benzyl, lower alkyl including methyl, ethyl, propyl;

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or $NR_2$ where R is acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl including methyl,ethyl, propyl, $CH_2R$ where R is methyl, halomethyl (fluoromethyl), ethyl, ethylenyl, or ethnyl; and

$R^3$ is hydrogen, a lower alkyl including, but limited to, methyl, halomethyl (fluoromethyl), ethyl, ethylenyl, or ethnyl.

21. A method for the preparation of a compound of formula 52B of claim 20 comprising mixing a compound of formula, 51B, wherein $R^1$, $R^2$, $R^3$, $R^4$ and $M^+$ are as defined in claim 20,



51B

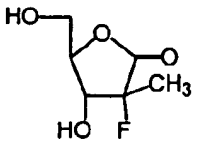
with a catalytic amount of acid and water in an appropriate solvent with or without a cosolvent.

22. The method of claim 21, wherein the acid is selected from one or more of the group consisting of HCl, $H_2PO_3$, $H_2SO_4$, TsOH, $CH_3CO_2H$, $CF_3CO_2H$, $HCO_2H$ and $RSO_3H$, wherein R is 4-methyl phenyl, phenyl, methyl, and ethyl.

23. The method of claim 21, wherein the solvent is selected from one or more of the group consisting of diethyl ether, tetrahydrofuran, dioxane, diglyme, toluene, MeCN, ethanol, benzene, and methanol.

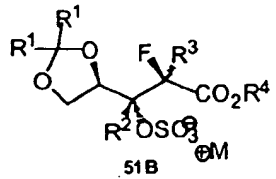
24. The method of claim 17, wherein the phase-transfer catalyst is selected from one or more of the group consisting of crown-ether, diglyme, and polyethylene glycol.

25. A process for the preparation of a compound of formula 53 comprising:

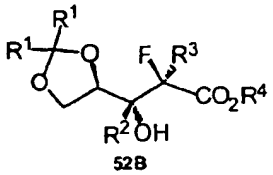


53

(a) treating a compound of the formula 51B or 52B:



51B



52B

with an acid in at least one solvent,

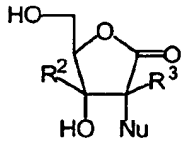
(b) optionally, followed by azeotropic distillation in benzene or toluene in

presence of acid.

26. The process of claim 25, wherein the acid from either step (a) or step (b) is selected from one or more of the group consisting of HCl, $H_2PO_3$, $H_2SO_4$, TsOH, $CH_3CO_2H$, $CF_3CO_2H$ and $HCO_2H$.

27. The process of claim 25, wherein the solvent from step (a) is selected from one or more of the group consisting of MeOH, EtOH, I-PrOH, $CH_3CN$, THF and water.

28. A compound of the following general formula **53B**:



53B

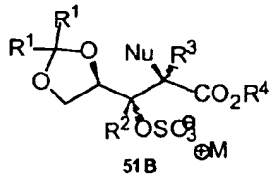
wherein,

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including, fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including, haloallyl (FHC=CH-$CH_2$-); and

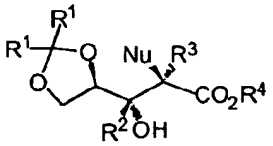
Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or NR where R is acyl including, acetyl, benzoyl, arylalkyl including benzyl, lower alkyl including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl including methyl, ethyl, or propyl.

29. A process for the preparation of a compound of the formula 53B comprising:

(a) heating a compound of the formula 51B or 52B:




51B




52B

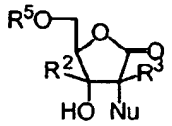
with an acid with a solvent; wherein the solvent is selected from one or more of the group consisting of MeOH, EtOH, i-PrOH, $CH_3CN$, THF, and water;

(b) optionally, followed by azeotropic distillation in benzene or toluene in presence of an acid.

30. The process of claim 29, wherein the acid from either step (a) or step (b) is selected from one or more of the group consisting of HCl, $H_2PO_3$, $H_2SO_4$, TsOH, $CH_3CO_2H$, $CF_3CO_2H$ and $HCO_2H$.

31. The process of claim 29, wherein the solvent is selected from one or more of the group consisting of MeOH, EtOH, I-PrOH, $CH_3CN$, THF and water.

32. A compound of the following general formula, **53C**:




**53C**

wherein,

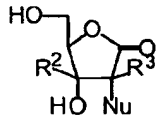
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R^5$ includes trityl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyloxymethyl, benzoyl, toluoyl, 4-phenyl benzoyl, 2-, 3-, or 4-nitrobenzoyl, 2-, 3-, or 4-chlorobenzoyl, other substituted benzoyl; and acyl with $C_{1-20}$ including benzoyl and pivaloyl; and

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or NR where R is acyl including, acetyl, benzoyl, arylalkyl including benzyl, lower alkyl ($C_{1-10}$) including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl ($C_{1-10}$) including methyl, ethyl, or propyl.

33. A process for the preparation of a compound of formula **53C** comprising

selective protection of the 5-hydroxy of the formula 53B:




**53B**

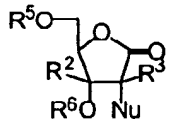
with a protecting agent, and a base in a solvent.

34. The process of claim 33, wherein the protecting agent is selected from one or more of the group consisting of trityl chloride, t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride, benzyloxymethyl chloride, acyl halide or acyl anhydride including but not limited to benzoyl chloride, toluoyl chloride, 4-phenyl benzoyl chloride, and benzoyl anhydride.

35. The process of claim 33, wherein the base is selected from one or more of the group consisting of imidazole, pyridine, 4-(dimethylamino)pyridine, triethytlamine, diisopropylethylamine, and 1,4- diazabicyclo[2,2,2]octane.

36. The process of claim 33, wherein the solvent is selected from one or more of the group consisting of pyridine, dichloromethane, chloroform, 1,2-dichloroethane, and tetrahydrofuran.

37. A compound of the following general formula, 49B:




**49B**

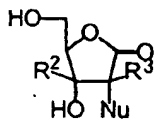
wherein

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R^5$ are independently methyl, benzyl, optionally substituted benzyl, trityl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, methoxymethyl (MOM), methoxyethyl (MEM), benzyloxymethyl (BOM), acetyl, benzoyl, 2-, 3-, or 4-nitrobenzoyl, 2-, 3-, or 4-chlorobenzoyl, toluoyl, or other substituted benzoyl; and acyl with $C_{1-20}$ including benzoyl and pivaloyl; and

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or $NR_2$ where R is independently acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl ($C_{1-10}$) including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl ($C_{1-10}$) including methyl, ethyl, or propyl.

38. A process for the preparation of a compound of formula, 49B of claim 35, comprising treating a compound 53B:



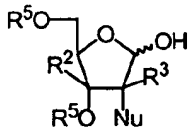
53B

with a protecting agent selected from one or more of the group consisting of methoxymethyl chloride, methoxyethyl chloride, benzyloxymethyl chloride, ethoxymethyl chloride, trityl chloride, triethylsilyl chloride, t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride, acetyl chloride, acetic, anhyride, benzoic anhydride, benzoyl chloride, toluoyl chloride, 4-phenyl, benzoyl chloride, 4-nitrobenzoyl chloride, and 4-chlorobenzoyl chloride; and a base in a solvent.

39. The process of claim 36, wherein the base is selected from one or more of the group consisting of imidazole, pyridine, 4-(dimethylamino)pyridine, triethytlamine, diisopropylethylamine, and 1,4- diazabicyclo[2,2,2]octane.

40. The process of claim 36, wherein the solvent is selected from one or more of the group consisting of pyridine, dichloromethane, chloroform, and 1,2-dichloroethane, and tetrahydrofuran and the like.

41. A compound of the following general formula, 56:



56

wherein

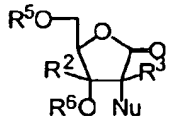
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R^5$ is methyl, benzyl, optionally substituted benzyl, trityl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, methoxymethyl (MOM),

methoxyethyl (MEM), benzyloxymethyl (BOM), acetyl, benzoyl, 2-, 3-, or 4-nitrobenzoyl, 2-, 3-, or 4-chlorobenzoyl, toluoyl, or other substituted benzoyl; and acyl with $C_{1-20}$ including benzoyl and pivaloyl; and

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or $NR_2$ where R is acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl including methyl, ethyl, or propyl.

42. A process for the preparation of a compound of formula 56 of claim 41 comprising treating a compound of the formula, 49B:




**49B**

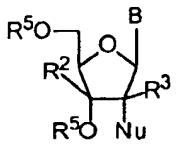
with a reducing agent in a solvent.

43. The process of claim 42, wherein the reducing agent is a metal hydride.

44. The process of claim 43, wherein the metal hydride is selected from one or more of the group consisting of DIBAL-H and lithium tri-*tert*-butoxyaluminum hydride.

45. The process of claim 42, wherein the solvent selected from one or more of the group consisting of dichloromethane, chloroform, benzene, toluene, and 1,2-dichloroethane.

46. A compound of the formula, 57:



57

wherein

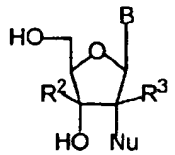
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R^5$ are independently methyl, benzyl, optionally substituted benzyl, trityl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, methoxymethyl (MOM), methoxyethyl (MEM), benzyloxymethyl (BOM), carbamate, carbonate, acetyl, benzoyl, 2-, 3-, or 4-nitrobenzoyl, 2-, 3-, or 4-chlorobenzoyl, toluoyl, or other substituted benzoyl; and acyl with $C_{1-20}$ including benzoyl and pivaloyl;

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or NR where R is acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl ($C_{1-10}$) including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl ($C_{1-10}$) including methyl, ethyl, or propyl; and

B is a natural or modified nucleic base .

47. A process for the preparation of a compound of the formula I:



I

wherein

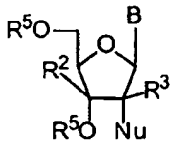
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C),

optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR or NR where R is acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl ($C_{6-10}$) including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl ($C_{6-10}$) including methyl, ethyl, or propyl; and

B is a natural or modified nucleic base;

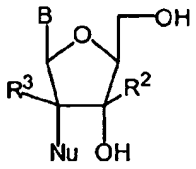
comprising treatment of a compound of the formula, **57**



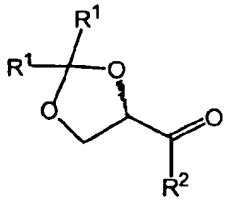
**57**

with alkyl ammonium fluoride, or, ammonium fluoride when $R^5$ is silyl; or acid when $R^5$ is trityl or alkoxymethyl; followed by sodium methoxide, or base, when $R^5$ is acyl.

48. A process for the preparation of the L-enantiomers, IB-L



**IB-L**



(S)-glyceraldehyde

wherein,

$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl, or $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively;

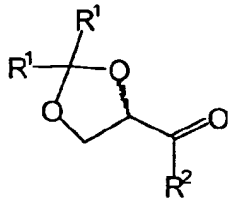
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl,

propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, OR or $NR_2$ where R is acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl including methyl, ethyl, propyl, $CH_2R$ where R is hydrogen, lower alkyl including methyl, ethyl, propyl; and

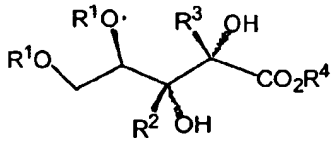
B is a natural or modified nucleic base,

comprising using the (S)-glyceraldehyde as the starting material.



(S)-glyceraldehyde

49. A process for the preparation of compounds of the formula I from claim 47 from the following intermediate:



**42B**

wherein

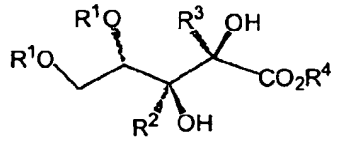
$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl; or $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively;

$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C),

optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and
$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including benzyl, lower alkyl ($C_{1-10}$) including methyl, ethyl, and propyl.

using the methods of any of the previous claims.

50. A process for the preparation of compounds of the formula, IB-L from claim 48 from the following intermediate:




**42B-L**

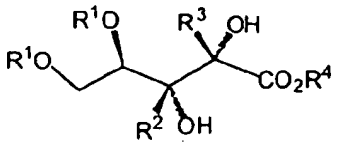
wherein

$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl; or $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively;
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and
$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including benzyl, lower alkyl ($C_{6-10}$) including methyl, ethyl, and propyl.

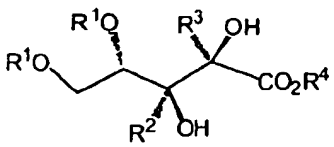
using the methods of any of the previous claims.

51. An intermediate of the formula 42B, 42B-L, 42C, 42D:

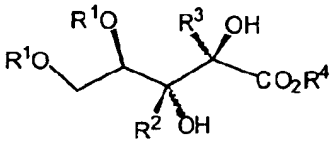
wherein



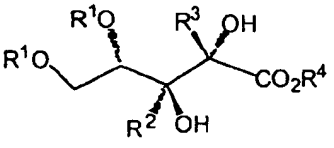

42B




42B-L




42C



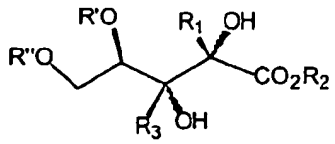

42D

$R^1$ is independently a lower alkyl ($C_1$-$C_6$) including methyl, ethyl, optionally substituted phenyl, optionally substituted benzyl; or $R^1$ is a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively;

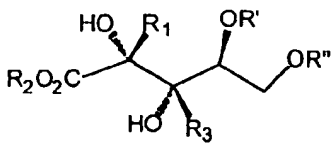
$R^2$, $R^3$ are independently hydrogen, a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and

$R^4$ is independently hydrogen, aryl including phenyl, aryl alkyl including benzyl, lower alkyl ($C_{1\text{-}10}$) including methyl, ethyl, and propyl.

52. A 2-alkyl-4,5-di-O-protected-2,3-dihydroxy-pentanoic-acid ester of the following general formula (42B) and its isomer (42B-L):




42B




42B-L

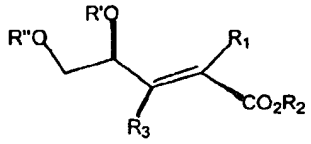
wherein R',R" = isopropylidene, benzylidene, cyclohexylidene or a like, or a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-

$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently lower alkyl of $C_1$-$C_6$, or aryl of $C_6$-$C_{20}$, benzyl and other optionally substituted benzyl, trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups; or H, acetyl, benzoyl and other optionally substituted acyl ( R' and R" are –C(O)-R, wherein R can be lower alkyl of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$, benzyl and other optionally substituted benzyl);

$R_1$, $R_2$ are independently hydrogen, aryl ($C_6$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and

$R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, but not limited to benzyl, lower alkyl ($C_{1\text{-}6}$) including methyl, ethyl, or propyl.

53. A process for the stereoselective preparation of a compound of formula **42B** of claim 51, mixing a compound of formula, **41**,




wherein R',R" = isopropylidene, benzylidene, cyclohexylidene or a like, or a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently lower alkyl of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$, benzyl and other optionally substituted benzyl), trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups or H, acetyl, benzoyl and other optionally substituted acyl ( R' and R" are –C(O)-R, wherein R can be independently lower alkyl of $C_1$-$C_6$, or aryl of $C_6$-$C_{20}$,benzyl and other optionally substituted benzyl); R' and R" can be independently lower alkyl of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$);

$R_1$, $R_2$ are independently hydrogen, aryl ($C_6$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including

fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and $R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, benzyl, lower alkyl ($C_{1-6}$) including methyl, ethyl, or propyl,

with a catalytic or stoichiometric amount of an osmium agent, without any chiral catalysts in a solvent.

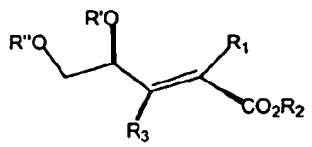
54. The process of claim 53, wherein the osmium agent is $OsO_4$, or osmate.

55. The process of claim 53, wherein the oxidant is selected from one or more of the group consisting of 4-N-methylmorpholine-N-oxide, pyridine-N-oxide trialkyamine-N-oxide, potassium fericyanide, hydrogen peroxide, chlorite, an alkyl peroxide an acyl peroxide, and a substituted or unsubstituted perbenzoic acid.

56. The process of claim 53, wherein the solvent is selected from one or more of the groups consisting of halogenated hydrocarbon including methylene chloride, chloroform, carbon tetrachloride, ethylene dichloride, dimethyl formamide, dimethyl acetamide, hexamethyl phosphoramide, water, tert-butanol, i-PrOH, THF, and pyridine.

57. A process for the stereoselective preparation of a compound of formula **42B** of claim 51, comprising:

mixing a compound of formula **41**




with an oxidant, in the presence of a catalytic or stoichiometric amount of an osmium agent, or potassium ruthenate, with a catalyst, and an inert solvent.

58. The process of claim 57, wherein the oxidant is selected from one or more of the group consisting of 4-N-methylmorpholine-N-oxide, trialkylamine-N-oxide, potassium ferricyanide, hydrogen peroxide, chlorite, an alkyl peroxide, an acyl and a substituted or unsubstituted perbenzoic acid.

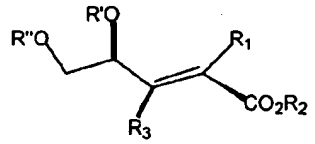
59. The process of claim 57, wherein the osmium agent is $OsO_4$ or osmate.

60. The process of claim 57, wherein the catatyst is selected from one or more of the group consisting of such as dihydroquinidine (DHQD) and its derivatives, dihydroquinine (DHQ) and its derivatives, quinuclidine, quinidine, DABCO, N,N'-dialkyl-2,2'-bipyrrolidine ligands, and N,N,N',N'-tetramethylethylenediamine.

61. The process of claim 57, wherein the solvent is selected from one or more of the group consisting of a halogenated hydrocarbon, dimethyl acetamide, hexamethyl phosphoramide, water, tert-butanol, i-PrOH, THF, and pyridine.

62. A process for the stereoselective preparation of a compound of formula **42B** of claim 51, comprising:

mixing a compound of formula **41**




with a permanganate compound, in suitable solvent, optionally with a base.

63. The process of claim 62, wherein the permanganate is selected from one or more of the group consisting of $KMnO_4$ tetradecyltrimethylammoium permanganate (TDTAP), cetyltrimethylammoium permanganate (CTAP) and other quaternary ammonium permanganate such as $R_1R_2R_3\ R_4N^+\ MnO_4^-$, wherein $R_1,R_2,R_3,R_4$, can be independently alkyl of $C_1$-$C_{20}$.

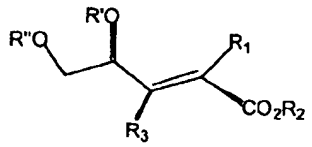
64. The process of claim 62, wherein the solvent is selected from one or more of the group consisting of a halogenated hydrocarbon, dimethyl acetamide, hexamethyl phosphoramide, water, tert-butanol, i-PrOH, THF, and pyridine.

65. The process of claim 64, wherein the halogenerated hydrocarbon is selected from one or more of the group consisting of methylene chloride, chloroform, carbon tetrachloride, ethylene dichloride.

66. The process of claim 63, wherein the base comprises KOH, NaOH, pyridine, and trialkylammonia.

67. A process for the stereoselective preparation of a compound of formula **42B** of claim 51, comprising:

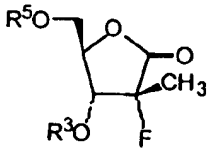
mixing a compound of formula **41**



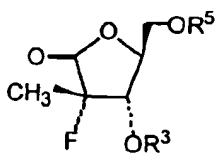

with a ruthenium system, optionally with a chiral or achiral catalyst in a solvent.

68. The process of claim 67, wherein the ruthenium system comprises $RuCl_3/CeCl_3/NaIO_4$.

69. A 3,5-di-O-protected-2-deoxy-2-fluoro-2-C-methyl-D-ribono-γ-lactone of the following general formula (49B) and its L-isomer (49B-L):




**49B**



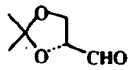

**49B-L**

wherein $R^3$ and $R^5$ can be independently H, $CH_3$, acetyl, benzoyl,, pivaloyl, or 4-nitrobenzoyl, 3-nitrobenzoyl, 2-nitrobenzoyl, 4-chlorobenzoyl, 3-

chlorobenzoyl, 2-chlorobenzoyl, 4-methylbenzoyl, 3-methylbenzoyl, 2-methylbenzoyl, para-phenylbenzoyl, and other optionally substituted acyl, –C(O)-R, where R can be independently lower alkyl of $C_1$-$C_{10,}$, or aryl of $C_6$-$C_{20}$, benzyl, 4-methoxybenzyl and other optionally substituted benzyl, trityl, trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups; alternatively, $R^3$ and $R^5$ are linked through -$SiR_2$-O-$SiR_2$- or -$SiR_2$-, wherein R is a lower alkyl such as $CH_3$, ethyl, and n-Pr or i-Pr.

70. A process for the preparation of the lactone of claim 69, comprising:

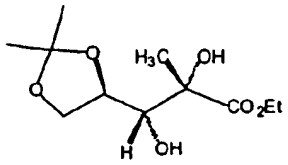
(a) reacting of a compound of the formula 39.




39

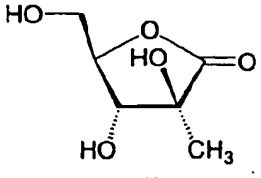
with (1-alkoxycarbonylethylidene) triphenylphosphorane under the Wittig condition in a solvent;

(b) stereoselective dihydroxylation of the olefin intermediate **41** to provide the diol **42** optionally or with chiral catalyst;



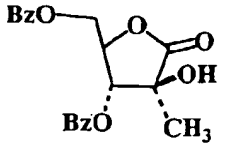

**42**

(c) treatment of the compound **42** with an acid in an alcohol to provide **46**;




**46**

(d) selective O-protection of primary and secondary OH groups to yield 3,5- di-O-protected derivative 47; and

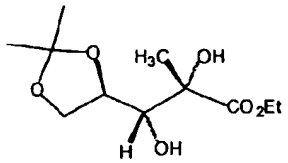


47

(e) fluorination of compound 47 to provide the desired lactone.

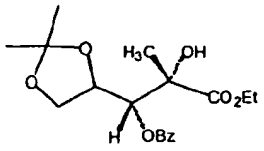
71. A process for the preparation of the lactone of claim 69, comprising:

(a) selective O-protected of secondary OH group of compound 42



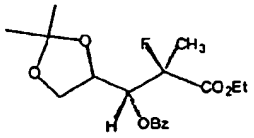
42

to yield the mono-O-protected derivative 43;



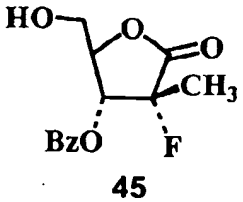
43

(b) fluorination of compound 43 to provide the fluorinated product 44;



44

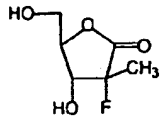
(c) lactonization of 44 with acid to give the γ lactone 45; and



45

(d) protection of the primary OH to provide the desired lactone.

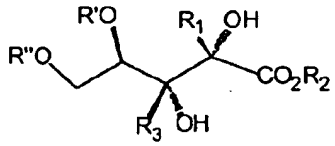
72. A method for the synthesis of an intermediate in the synthesis of a lactone **53**,



**53**

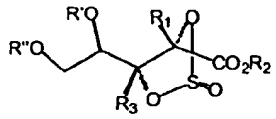
comprising:

(a) mixing a compound of formula, **42B**,



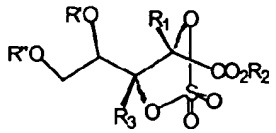
**42B**

with thionyl chloride or thionyl diimidazole in presence of a base in a solvent to yield the intermediate **50A;**



**50A**

73. A process for preparation of a compound of formula **50B** comprising,



**50B**

wherein R',R" = isopropylidene or cyclohexylidene or a like, or a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups or H, acetyl, benzoyl and other optionally substituted acyl ( R' and R" are –C(O)-R,

wherein R can be lower alkyl of $C_1$-$C_{6,}$, or aryl of $C_6$-$C_{20}$,benzyl and other optionally substituted benzyl); R' and R" can be independently lower alkyl of $C_1$-$C_{6,}$, or aryl of $C_6$-$C_{20}$);

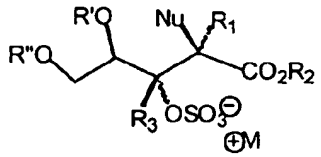
$R_1$, $R_2$ are independently hydrogen, aryl ($C_6$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and

$R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, but not limited to benzyl, lower alkyl ($C_{1-6}$) including methyl, ethyl, or propyl; comprising mixing the product **50A** from claim 70 with an oxidant in a solvent or a combination of solvents; or

alternatively, mixing a compound of the formula, **42B** of claim 51, with sulfuryl chloride or sulfuryl diimidazole in presence of a base, in a solvent.

74. The process of claim 73, whrein the oxidant is selected from one or more of group consisting of $RuCl_3$, $KMnO_4$, TEMPO, $NaIO_4$, $KIO_4$, $HIO_4$, mCPBA, NaOCl and oxone.

75. A compound of the following general formula **51B**:




**51B**

wherein R',R" is isopropylidene or cyclohexylidene or a like, or a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups or H, acetyl, benzoyl and other optionally substituted acyl ( R' and R" are –C(O)-R, wherein R can be lower alkyl

of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$,benzyl and other optionally substituted benzyl); R' and R" can be independently lower alkyl of $C_1$-$C_6$, , or aryl of $C_6$-$C_{20}$);

$R_1$, $R_2$ are independently hydrogen, aryl ($C_6$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, to benzyl, lower alkyl ($C_{1-6}$) including methyl, ethyl, or propyl; d

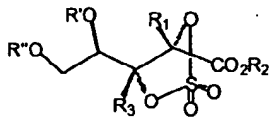
Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR, NR'", NHR'", or NR'"$_2$ wherein R'" is H or acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl

($C_{6-10}$) including methyl, ethyl, propyl, $CH_2R$ wherein R is hydrogen, lower alkyl ($C_{1-10}$) including methyl, ethyl, or propyl; and

$M^+$ is tetraalkylammonium including tetrabutylammonium, tetraethylammonium, tetramethylammonium, or metal cation including sodium, potassium, cesium, rubidium, and silver cations.

76. A process for the preparation of compounds of the general formula **51B** of claim 75, comprising:

(a) mixing a compound of the following formula, **50B**




**50B**

wherein R',R" = isopropylidene or cyclohexylidene or a like, or a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups or H, acetyl, benzoyl and other optionally substituted acyl ( R' and R" are –C(O)-R,

wherein R can be lower alkyl of $C_1$-$C_{6,}$, or aryl of $C_6$-$C_{20}$,benzyl and other optionally substituted benzyl); R' and R" can be independently lower alkyl of $C_1$-$C_{6,}$, or aryl of $C_6$-$C_{20}$);

$R_1$, $R_2$ are independently hydrogen, aryl ($C_6$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$); including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-); and $R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, *o*-benzyl, lower alkyl ($C_{1\text{-}6}$) including methyl, ethyl, or propyl;

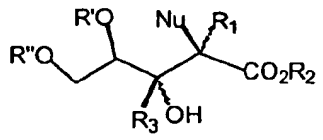
with one fluoride source or in combination with phase transfer catalyst in a solvent; or

(b) alternatively mixing a compound of the formula, **50B** with a base.

77. The process of claim 76, wherein the base is selected from one or more of the group consisting of $NaBH_4$, tetraalkylammonium chloride, tetraalkylammonium bromide, $NaN_3$ or $LiN_3$,$NH_4SCN$, $CF_3I$-tetrakis (dimethylamino)-ethylene (TDAE), tetraalkylammonium nitrate, KCN, $NH_4OR$, HNR where R is lower alkyl or acyl, $LiCu(R)_2$ where R is methyl, ethyl, ethylenyl, or ethnyl.

78. The method of claim 75, wherein the fluoride source is selected from the group consisting of tetramethylammonium fluoride (TMAF), tetraethylammonium fluoride (TEAF), tetrabutylammonium fluoride (TBAF),tris(dimehtylamino)sulfur (trimethylsilyl)difluoride (TAS-F), alone or in combination with a fluoride source selected from one or more of the group consisting of silver fluroide (AgF), potassium fluoride (KF), cesium fluoride (CsF), and rubidium fluoride (RbF); optionally in combination with crown-ether, diglyme, polyethylene glycol or other phase transfer catalyst.

79. A compound of the following general formula **52B**:




**52B**

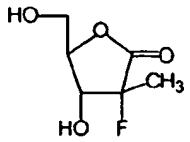
wherein R',R" = isopropylidene, benzylidene, cyclohexylidene or a like, or a part of cyclic group including ethylene (-$CH_2CH_2$-), or trimethylene (-$CH_2CH_2CH_2$-) forming cyclopentyl or cyclohexanyl group, respectively; R' and R" can be independently trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups or H, acetyl, benzoyl and other optionally substituted acyl (R' and R" are –C(O)-R, wherein R can be independently lower alkyl of $C_1$-$C_6$, , or aryl of $C_7$-$C_{20}$,benzyl and other optionally substituted benzyl); R' and R" can be independently lower alkyl of $C_1$-$C_6$,, or aryl of $C_7$-$C_{20}$);

$R_1$, $R_2$ are independently hydrogen, aryl ($C_7$-$C_{20}$) and a lower alkyl ($C_1$-$C_6$) including methyl, hydroxymethyl, methoxymethyl, halomethyl including fluoromethyl, ethyl, propyl, optionally substituted ethenyl including vinyl, halovinyl (F-CH=C), optionally substituted ethnyl including haloethnyl (F-C≡C), optionally substituted allyl including haloallyl (FHC=CH-$CH_2$-);

$R_3$ is independently hydrogen, aryl including phenyl, aryl alkyl including, benzyl, lower alkyl ($C_{1\text{-}6}$) including methyl, ethyl, or propyl; and

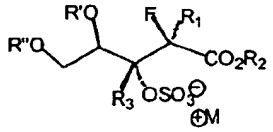
Nu is halogen (F, Cl, Br), $N_3$, CN, $NO_3$, $CF_3$, SCN, OR, NR'", NHR'", or NR'"$_2$ where R'" is H or acyl including acetyl, benzoyl, arylalkyl including benzyl, lower alkyl ($C_{6\text{-}10}$) including methyl,ethyl, propyl, $CH_2R$ where R is methyl, halomethyl (fluoromethyl), ethyl, ethylenyl, or ethnyl.

80. A process for the preparation of a compound of formula **53** comprising:

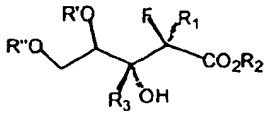


53

(a) heating a compound of the formula **51B** or **52B**:



51B



52B

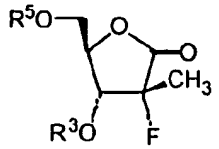
with an acid in a solvent or a combination of solvents;

(b) optionally, followed by azeotropic distillation in benzene or toluene in presence of an acid.

81. The process of claim 80, wherein the acid is selected from one or more of the group consisting of acidic polymer resins, HCl, $H_2PO_3$, $H_2SO_4$, TsOH, $CH_3CO_2H$, $CF_3CO_2H$, and $HCO_2H$.

82. The process of claim 80, wherein the solvent is selected from one or more of the group consisting of MeOH, EtOH, i-PrOH, $CH_3CN$, THF, and water.

83. A process for the preparation of a compound of the formula **49B**:



**49B**

wherein $R^3$ and $R^5$ can be independently H, $CH_3$, acetyl, benzoyl, pivaloyl or 4-nitrobenzoyl, 3-nitrobenzoyl, 2-nitrobenzoyl, 4-chlorobenzoyl, 3-chlorobenzoyl, 2-chlorobenzoyl, 4-methylbenzoyl, 3-methylbenzoyl, 2-methylbenzoyl, para-phenylbenzoyl, and other optionally substituted acyl ($R^3$ and $R^5$ are –C(O)-R, wherein R can be lower alkyl of $C_1$-$C_{10}$, , or aryl of $C_6$-$C_{20}$, benzyl, 4-methoxybenzyl and other optionally substituted benzyl; $R^3$ and $R^5$ can be independently aryl of $C_6$-$C_{20}$, trityl, trialkylsilyl, *t*-butyl-dialkylsyl, *t*-butyldiphenylsilyl, TIPDS, THP, MOM, MEM and other optionally ether protecting groups; and alternatively, $R^{3'}$ and $R^{5'}$ are linked through -$SiR_2$-O-$SiR_2$- or -$SiR_2$-, wherein R is a lower alkyl such as $CH_3$, ethyl, and n-Pr or I-Pr;

comprising protection of the hydroxy groups of the formula 53 with a protecting agent selected from one or more of the group consisting of trityl chloride, t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride, benzyloxymethyl chloride, acyl halide or acyl anhydride including benzoyl chloride, toluoyl chloride, 4-phenyl benzoyl chloride, benzoyl anhydride, with a base in a solvent.